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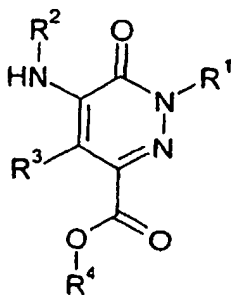
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(54) Title: **PYRIDAZIN-3(2H)-ONE DERIVATIVES AND THEIR USE AS PDE4 INHIBITORS**



(I)

(57) Abstract: The invention relates to new therapeutically useful pyridazin-3(2H)-one derivatives of Formula (I) and to pharmaceutical compositions containing them. These compounds are potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are thus useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be susceptible of being improved by inhibition of PDE4 such as asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

## PYRIDAZIN-3 (2H)-ONE DERIVATIVES AND THEIR USE AS PDE4 INHIBITORS

The present invention relates to new therapeutically useful pyridazin-3(2H)-one derivatives, to processes for their preparation and to pharmaceutical compositions  
5 containing them. These compounds are potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are thus useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be susceptible of being improved by inhibition of PDE4.

10 Phosphodiesterases (PDEs) comprise a superfamily of enzymes responsible for the hydrolysis and inactivation of the second messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Eleven different PDE families have been identified to date (PDE1 to PDE11) which differ in substrate preference, catalytic activity, sensitivity to endogenous activators and inhibitors, and  
15 encoding genes.

The PDE4 isoenzyme family exhibits a high affinity for cyclic AMP but has weak affinity for cyclic GMP. Increased cyclic AMP levels caused by PDE4 inhibition are associated with the suppression of cell activation in a wide range of inflammatory and  
20 immune cells, including lymphocytes, macrophages, basophils, neutrophils, and eosinophils. Moreover, PDE4 inhibition decreases the release of the cytokine Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ). The biology of PDE4 is described in several recent reviews, for example M. D. Houslay, *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, 69, 249-315; J. E. Souness et al. *Immunopharmacol.* **2000** 47, 127-162; or M. Conti and S. L. Jin, *Prog.*  
25 *Nucleic Acid Res. Mol. Biol.* **1999**, 63, 1-38.

In view of these physiological effects, PDE4 inhibitors of varied chemical structures have been recently disclosed for the treatment or prevention of chronic and acute inflammatory diseases and of other pathological conditions, diseases and disorders  
30 known to be susceptible to amelioration by inhibition of PDE4. See, for example, US 5449686, US 5710170, WO 98/45268, WO 99/06404, WO 01/57025, WO 01/57036, WO 01/46184, WO 97/05105, WO 96/40636, WO03/097613, US 5786354, US 5773467, US 5753666, US 5728712, US 5693659, US 5679696, US 5596013, US 5541219, US 5508300, US 5502072 or H. J. Dyke and J. G. Montana, *Exp. Opin. Invest. Drugs* **1999**, 8,  
35 1301-1325.

A few compounds having the capacity to selectively inhibit phosphodiesterase 4 are in active development. Examples of these compounds are cipamfylline, arofyline, cilomilast, roflumilast, mesopram and pumafentrine.

5

The international applications WO03/097613 A1, WO2004/058729 A1 and WO 2005/049581 describe pyridazin-3(2H)-one derivatives as potent and selective inhibitors of PDE4. We have now found that the compounds of formula (I) described in more detail below have surprising and particularly advantageous properties.

10

It is known that the clinical developement in man of early PDE4 inhibitors such as rolipram has been hampered by the appearance of side effects such as nausea and vomiting at therapeutic plasma levels (Curr. Pharm. Des. 2002, 8,1255-96). The compounds described in the present invention are potent and selective PDE4 inhibitors which are hydrolized systemically. This particular property provides the compounds with a high local activity and little or no systemic action, avoiding or reducing the risk of unwanted systemic side effects, and makes them useful for the treatment or prevention of these pathological conditions, diseases and disorders, in particular asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

20

The compounds of the present invention can also be used in combination with other drugs known to be effective in the treatment of these diseases. For example, they can be used in combination with steroids or immunosuppressive agents, such as cyclosporin A, rapamycin, T-cell receptor blockers,  $\beta$ 2-adrenergic agonists or antagonists of M3 muscarinic receptors. In this case the administration of the compounds allows a reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

25

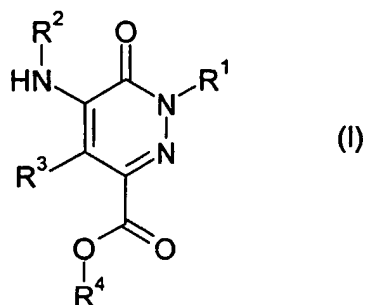
Like other PDE4 inhibitors (see references above) the compounds of the invention can also be used for blocking the ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids. They can be used alone or in combination with antacids and/or antisecretory drugs in the preventive

30

and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage  
 5 to the cells or tissues is produced through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue  
 10 repair and wound healing.

Accordingly, the present invention provides novel compounds of formula (I):



15 wherein

R¹ represents:

- a hydrogen atom;
- an alkyl, alkenyl or alkynyl group, which is optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl,  
 20 alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups;

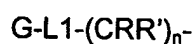
R² represents a monocyclic or polycyclic heteroaryl group, which is optionally substituted by one or more substituents selected from:

- 25 • halogen atoms;
- alkyl and alkylene groups, which are optionally substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups

- phenyl, hydroxy, hydroxycarbonyl, hydroxyalkyl, alkoxycarbonyl, alkoxy, cycloalkoxy, nitro, cyano, aryloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, acyl, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulfamido, aminosulfonyl, mono- or di-alkylaminosulfonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

R<sup>3</sup> represents a hydrogen atom or an alkylcarbonyl group wherein the alkyl group may be substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl groups

R<sup>4</sup> represents a group of formula:



wherein

n is an integer from 0 to 3

R and R' are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

L1 is a linker selected from the group consisting of a direct bond, a -O-, -CO-, -NR"-, -O(CO)NR"-, -O(CO)O-, -O-(CO)-, -(CO)O-, -NR"-(CO)- and -O(R"O)(PO)O- groups wherein R" is selected from the group consisting of hydrogen atoms and lower alkyl groups, preferably L1 is selected from the group consisting of a direct bond, an oxygen atom, a -CO-, -NR"-, -O(CO)NR"-, -O(CO)O-, -O-(CO)-, R"N-(CO)- and -O(R"O)(PO)O- groups

G is selected from hydrogen atoms and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl and heteroaryl groups said groups being optionally substituted with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more substituents selected from halogen atoms; and
- hydroxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, amino, mono- or di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido,

N',N'-dialkylureido, alkylsulfamido, aminosulphonyl, mono- or di-alkylaminosulfonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

and the pharmaceutically acceptable salts or N-oxides thereof

5

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by inhibition of PDE4; and methods of treatment of diseases susceptible to amelioration by inhibition of PDE4, which methods  
10 comprise the administration of the compounds of the invention to a subject in need of treatment.

As used herein the term alkyl embraces optionally substituted, linear or branched  
15 radicals having 1 to 20 carbon atoms or, preferably 1 to 12 carbon atoms. More preferably alkyl radicals are "lower alkyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl, t-butyl, n-  
20 pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl, 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylpentyl and iso-hexyl radicals.

As used herein, the term alkenyl embraces optionally substituted, linear or  
25 branched, mono or polyunsaturated radicals having 1 to 20 carbon atoms or, preferably, 1 to 12 carbon atoms. More preferably alkenyl radicals are "lower alkenyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular it is preferred that the alkenyl radicals are mono or diunsaturated.

30

Examples include vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl and 4-pentenyl radicals.

As used herein, the term alkynyl embraces optionally substituted, linear or  
35 branched, mono or polyunsaturated radicals having 1 to 20 carbon atoms or, preferably, 1

to 12 carbon atoms. More preferably, alkynyl radicals are "lower alkynyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular, it is preferred that the alkynyl radicals are mono or diunsaturated.

5           Examples include 1-propynyl, 2-propynyl, 1-butyne, 2-butyne and 3-butyne radicals.

          When it is mentioned that alkyl, alkenyl or alkynyl radicals may be optionally substituted it is meant to include linear or branched alkyl, alkenyl or alkynyl radicals as  
10   defined above, which may be unsubstituted or substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different.

          A said optionally substituted alkenyl group is typically unsubstituted or  
15   substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkenyl group are themselves unsubstituted.

20           A said optionally substituted alkynyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkynyl group are themselves unsubstituted.

25           A said optionally substituted alkyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkyl group  
30   are themselves unsubstituted. Preferred optionally substituted alkyl groups are unsubstituted or substituted with 1, 2 or 3 fluorine atoms.

          As used herein, the term alkylene embraces divalent alkyl moieties typically having from 1 to 6, for example from 1 to 4, carbon atoms. Examples of C<sub>1</sub>-C<sub>4</sub> alkylene

radicals include methylene, ethylene, propylene, butylene, pentylene and hexylene radicals.

A said optionally substituted alkylene group is typically unsubstituted or  
5 substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms.

When an alkylene radical is present as a substituent on another radical it shall  
10 be deemed to be a single substituent, rather than a radical formed by two substituents.

As used herein, the term alkoxy (or alkyloxy) embraces optionally substituted, linear or branched oxy-containing radicals each having alkyl portions of 1 to 10 carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having 1 to 8, preferably  
15 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkoxy group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having  
20 from 1 to 4 carbon atoms. Typically, the substituents on an alkoxy group are themselves unsubstituted.

Preferred alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-  
25 hydroxyethoxy and 2-hydroxypropoxy.

As used herein, the term alkylthio embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having  
30 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

An alkylthio group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having

from 1 to 4 carbon atoms. Typically, the substituents on an alkythio group are themselves unsubstituted.

Preferred optionally substituted alkythio radicals include methylthio, ethylthio, n-  
5 propylthio, i-propylthio, n-butylthio, sec-butylthio, t-butylthio, trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio and 2-hydroxypropylthio.

As used herein, the term monoalkylamino embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached  
10 to a divalent -NH- radical. More preferred monoalkylamino radicals are "lower monoalkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylamino group typically contains an alkyl group which is unsubstituted  
15 or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylamino group are themselves unsubstituted.

20 Preferred optionally substituted monoalkylamino radicals include methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, sec-butylamino, t-butylamino, trifluoromethylamino, difluoromethylamino, hydroxymethylamino, 2-hydroxyethylamino and 2-hydroxypropylamino.

25 As used herein, the term dialkylamino embraces radicals containing a trivalent nitrogen atoms with two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached thereto. More preferred dialkylamino radicals are "lower dialkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

30

A dialkylamino group typically contains two alkyl groups, each of which is unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the  
35 substituents on a dialkylamino group are themselves unsubstituted.

Preferred optionally substituted dialkylamino radicals include dimethylamino, diethylamino, methyl(ethyl)amino, di(n-propyl)amino, n-propyl(methyl)amino, n-propyl(ethyl)amino, di(i-propyl)amino, i-propyl(methyl)amino, i-propyl(ethyl)amino, di(n-butyl)amino, n-butyl(methyl)amino, n-butyl(ethyl)amino, n-butyl(i-propyl)amino, di(sec-butyl)amino, sec-butyl(methyl)amino, sec-butyl(ethyl)amino, sec-butyl(n-propyl)amino, sec-butyl(i-propyl)amino, di(t-butyl)amino, t-butyl(methyl)amino, t-butyl(ethyl)amino, t-butyl(n-propyl)amino, t-butyl(i-propyl)amino, trifluoromethyl(methyl)amino, trifluoromethyl(ethyl)amino, trifluoromethyl(n-propyl)amino, trifluoromethyl(i-propyl)amino, trifluoromethyl(n-butyl)amino, trifluoromethyl(sec-butyl)amino, difluoromethyl(methyl)amino, difluoromethyl(ethyl)amino, difluoromethyl(n-propyl)amino, difluoromethyl(i-propyl)amino, difluoromethyl(n-butyl)amino, difluoromethyl(sec-butyl)amino, difluoromethyl(t-butyl)amino, difluoromethyl(trifluoromethyl)amino, hydroxymethyl(methyl)amino, ethyl(hydroxymethyl)amino, hydroxymethyl(n-propyl)amino, hydroxymethyl(i-propyl)amino, n-butyl(hydroxymethyl)amino, sec-butyl(hydroxymethyl)amino, t-butyl(hydroxymethyl)amino, difluoromethyl(hydroxymethyl)amino, hydroxymethyl(trifluoromethyl)amino, hydroxyethyl(methyl)amino, ethyl(hydroxyethyl)amino, hydroxyethyl(n-propyl)amino, hydroxyethyl(i-propyl)amino, n-butyl(hydroxyethyl)amino, sec-butyl(hydroxyethyl)amino, t-butyl(hydroxyethyl)amino, difluoromethyl(hydroxyethyl)amino, hydroxyethyl(trifluoromethyl)amino, hydroxypropyl(methyl)amino, ethyl(hydroxypropyl)amino, hydroxypropyl(n-propyl)amino, hydroxypropyl(i-propyl)amino, n-butyl(hydroxypropyl)amino, sec-butyl(hydroxypropyl)amino, t-butyl(hydroxypropyl)amino, difluoromethyl(hydroxypropyl)amino, hydroxypropyl(trifluoromethyl)amino.

As used herein, the term hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals.

Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

As used herein, the term alkoxycarbonyl embraces optionally substituted, linear or branched radicals each having alkyl portions of 1 to 10 carbon atoms and attached to

an oxycarbonyl radical. More preferred alkoxycarbonyl radicals are "lower alkoxycarbonyl" radicals, in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

5           An alkoxycarbonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkoxycarbonyl group are themselves unsubstituted.

10

Preferred optionally substituted alkoxycarbonyl radicals include methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, i-propoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, t-butoxycarbonyl, trifluoromethoxycarbonyl, difluoromethoxycarbonyl, hydroxymethoxycarbonyl, 2-hydroxyethoxycarbonyl and 2-  
15 hydroxypropoxycarbonyl.

As used herein, the term monoalkylcarbamoyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to the nitrogen of a-NHCO- radical. More preferred monoalkylcarbamoyl radicals  
20 are "lower monoalkylcarbamoyl" radicals in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylcarbamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably  
25 selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylcarbamoyl group are themselves unsubstituted.

Preferred optionally substituted monoalkylcarbamoyl radicals include  
30 methylcarbamoyl, ethylcarbamoyl, n-propylcarbamoyl, i-propylcarbamoyl, n-butylcarbamoyl, sec-butylcarbamoyl, t-butylcarbamoyl, trifluoromethylcarbamoyl, difluoromethylcarbamoyl, hydroxymethylcarbamoyl, 2-hydroxyethylcarbamoyl and 2-hydroxypropylcarbamoyl.

As used herein, the term dialkylcarbamoyl embraces radicals containing a radical NCO- where the nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred dialkylcarbamoyl radicals are "lower dialkylcarbamoyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A dialkylcarbamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a dialkylcarbamoyl group are themselves unsubstituted.

Preferred optionally substituted dialkylcarbamoyl radicals include dimethylcarbamoyl, diethylcarbamoyl, methyl(ethyl)carbamoyl, di(n-propyl)carbamoyl, n-propyl(methyl)carbamoyl, n-propyl(ethyl)carbamoyl, di(i-propyl)carbamoyl, i-propyl(methyl)carbamoyl, i-propyl(ethyl)carbamoyl, di(n-butyl)carbamoyl, n-butyl(methyl)carbamoyl, n-butyl(ethyl)carbamoyl, n-butyl(i-propyl)carbamoyl, di(sec-butyl)carbamoyl, sec-butyl(methyl)carbamoyl, sec-butyl(ethyl)carbamoyl, sec-butyl(n-propyl)carbamoyl, sec-butyl(i-propyl)carbamoyl, di(t-butyl)carbamoyl, t-butyl(methyl)carbamoyl, t-butyl(ethyl)carbamoyl, t-butyl(n-propyl)carbamoyl, t-butyl(i-propyl)carbamoyl, trifluoromethyl(methyl)carbamoyl, trifluoromethyl(ethyl)carbamoyl, trifluoromethyl(n-propyl)carbamoyl, trifluoromethyl(i-propyl)carbamoyl, trifluoromethyl(n-butyl)carbamoyl, trifluoromethyl(sec-butyl)carbamoyl, difluoromethyl(methyl)carbamoyl, difluoromethyl(ethyl)carbamoyl, difluoromethyl(n-propyl)carbamoyl, difluoromethyl(i-propyl)carbamoyl, difluoromethyl(n-butyl)carbamoyl, difluoromethyl(sec-butyl)carbamoyl, difluoromethyl(t-butyl)carbamoyl, difluoromethyl(trifluoromethyl)carbamoyl, hydroxymethyl(methyl)carbamoyl, ethyl(hydroxymethyl)carbamoyl, hydroxymethyl(n-propyl)carbamoyl, hydroxymethyl(i-propyl)carbamoyl, n-butyl(hydroxymethyl)carbamoyl, sec-butyl(hydroxymethyl)carbamoyl, t-butyl(hydroxymethyl)carbamoyl, difluoromethyl(hydroxymethyl)carbamoyl, hydroxymethyl(trifluoromethyl)carbamoyl, hydroxyethyl(methyl)carbamoyl, ethyl(hydroxyethyl)carbamoyl, hydroxyethyl(n-propyl)carbamoyl, hydroxyethyl(i-propyl)carbamoyl, n-butyl(hydroxyethyl)carbamoyl, sec-butyl(hydroxyethyl)carbamoyl, t-butyl(hydroxyethyl)carbamoyl, difluoromethyl(hydroxyethyl)carbamoyl, hydroxyethyl(trifluoromethyl)carbamoyl, hydroxypropyl(methyl)carbamoyl, ethyl(hydroxypropyl)carbamoyl, hydroxypropyl(n-

propyl)carbamoyl, hydroxypropyl(i-propyl)carbamoyl, n-butyl(hydroxypropyl)carbamoyl, sec-butyl(hydroxypropyl)carbamoyl, t-butyl(hydroxypropyl)carbamoyl, difluoromethyl(hydroxypropyl)carbamoyl, hydroxypropyl(trifluoromethyl)carbamoyl.

5           As used herein, the term alkylsulfinyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent  $-SO-$  radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

10           An alkylsulfinyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a alkylsulfinyl group are themselves unsubstituted.

15           Preferred optionally substituted alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, i-propylsulfinyl, n-butylsulfinyl, sec-butylsulfinyl, t-butylsulfinyl, trifluoromethylsulfinyl, difluoromethylsulfinyl, hydroxymethylsulfinyl, 2-hydroxyethylsulfinyl and 2-hydroxypropylsulfinyl.

20           As used herein, the term alkylsulfonyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached to a divalent  $-SO_2-$  radical. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

25           An alkylsulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylaminosulfonyl group  
30 are themselves unsubstituted.

          As used herein, the term monoalkylaminosulfonyl embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to the nitrogen of a  $-NH-SO_2-$  radical. More preferred monoalkylaminosulfonyl

radicals are "lower monoalkylaminosulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

A monoalkylaminosulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a monoalkylaminosulfonyl group are themselves unsubstituted.

Preferred optionally substituted monoalkylaminosulfonyl radicals include methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, i-propylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, t-butylaminosulfonyl, trifluoromethylaminosulfonyl, difluoromethylaminosulfonyl, hydroxymethylaminosulfonyl, 2-hydroxyethylaminosulfonyl and 2-hydroxypropylaminosulfonyl.

As used herein, the term dialkylaminosulfonyl embraces radicals containing a radical  $\text{NSO}_2\cdot$  where the nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred dialkylaminosulfonyl radicals are "lower dialkylaminosulfonyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

A dialkylaminosulfonyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a dialkylaminosulfonyl group are themselves unsubstituted.

Preferred optionally substituted dialkylaminosulfonyl radicals include dimethylaminosulfonyl, diethylaminosulfonyl, methyl(ethyl)aminosulfonyl, di(n-propyl)aminosulfonyl, n-propyl(methyl)aminosulfonyl, n-propyl(ethyl)aminosulfonyl, di(i-propyl)aminosulfonyl, i-propyl(methyl)aminosulfonyl, i-propyl(ethyl)aminosulfonyl, di(n-butyl)aminosulfonyl, n-butyl(methyl)aminosulfonyl, n-butyl(ethyl)aminosulfonyl, n-butyl(i-propyl)aminosulfonyl, di(sec-butyl)aminosulfonyl, sec-butyl(methyl)aminosulfonyl, sec-butyl(ethyl)aminosulfonyl, sec-butyl(n-propyl)aminosulfonyl, sec-butyl(i-propyl)aminosulfonyl, di(t-butyl)aminosulfonyl, t-butyl(methyl)aminosulfonyl, t-

butyl(ethyl)aminosulfonyl, t-butyl(n-propyl)aminosulfonyl, t-butyl(i-propyl)aminosulfonyl, trifluoromethyl(methyl)aminosulfonyl, trifluoromethyl(ethyl)aminosulfonyl, trifluoromethyl(n-propyl)aminosulfonyl, trifluoromethyl(i-propyl)aminosulfonyl, trifluoromethyl(n-butyl)aminosulfonyl, trifluoromethyl(sec-butyl)aminosulfonyl,

5 difluoromethyl(methyl)aminosulfonyl, difluoromethyl(ethyl)aminosulfonyl, difluoromethyl(n-propyl)aminosulfonyl, difluoromethyl(i-propyl)aminosulfonyl, difluoromethyl(n-butyl)aminosulfonyl, difluoromethyl(sec-butyl)aminosulfonyl, difluoromethyl(t-butyl)aminosulfonyl, difluoromethyl(trifluoromethyl)aminosulfonyl,

hydroxymethyl(methyl)aminosulfonyl, ethyl(hydroxymethyl)aminosulfonyl,

10 hydroxymethyl(n-propyl)aminosulfonyl, hydroxymethyl(i-propyl)aminosulfonyl, n-butyl(hydroxymethyl)aminosulfonyl, sec-butyl(hydroxymethyl)aminosulfonyl, t-butyl(hydroxymethyl)aminosulfonyl, difluoromethyl(hydroxymethyl)aminosulfonyl, hydroxymethyl(trifluoromethyl)aminosulfonyl, hydroxyethyl(methyl)aminosulfonyl, ethyl(hydroxyethyl)aminosulfonyl, hydroxyethyl(n-propyl)aminosulfonyl, hydroxyethyl(i-

15 propyl)aminosulfonyl, n-butyl(hydroxyethyl)aminosulfonyl, sec-butyl(hydroxyethyl)aminosulfonyl, t-butyl(hydroxyethyl)aminosulfonyl, difluoromethyl(hydroxyethyl)aminosulfonyl, hydroxyethyl(trifluoromethyl)aminosulfonyl, hydroxypropyl(methyl)aminosulfonyl, ethyl(hydroxypropyl)aminosulfonyl, hydroxypropyl(n-propyl)aminosulfonyl, hydroxypropyl(i-propyl)aminosulfonyl, n-

20 butyl(hydroxypropyl)aminosulfonyl, sec-butyl(hydroxypropyl)aminosulfonyl, t-butyl(hydroxypropyl)aminosulfonyl, difluoromethyl(hydroxypropyl)aminosulfonyl and hydroxypropyl(trifluoromethyl)aminosulfonyl.

As used herein, the term alkylsulfamoyl embraces radicals containing an

25 optionally substituted, linear or branched alkyl radical of 1 to 10 carbon atoms and attached to the nitrogen of a-NSO<sub>2</sub>- radical. More preferred alkylsulfamoyl radicals are "lower alkylsulfamoyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

30 An alkylsulfamoyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkylsulfamoyl group are themselves unsubstituted.

Preferred optionally substituted alkylsulfamoyl radicals include methylsulfamoyl, ethylsulfamoyl, n-propylsulfamoyl, i-propylsulfamoyl, n-butylsulfamoyl, sec-butylsulfamoyl, t-butylsulfamoyl, trifluoromethylsulfamoyl, difluoromethylsulfamoyl, hydroxymethylsulfamoyl, 2-hydroxyethylsulfamoyl and 2-hydroxypropylsulfamoyl.

5

As used herein, the term alkylsulfamido embraces radicals containing an optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms and attached to one of the nitrogen atoms of a  $\text{-NHSO}_2\text{NH-}$  radical. More preferred alkylsulfamido radicals are "lower alkylsulfamido" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

10

An alkylsulfamido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an alkylsulfamido group are themselves unsubstituted.

15

Preferred optionally substituted alkylsulfamido radicals include methylsulfamido, ethylsulfamido, n-propylsulfamido, i-propylsulfamido, n-butylsulfamido, sec-butylsulfamido, t-butylsulfamido, trifluoromethylsulfamido, difluoromethylsulfamido, hydroxymethylsulfamido, 2-hydroxyethylsulfamido and 2-hydroxysulfamido.

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As used herein, the term N'-alkylureido embraces radicals containing an optionally substituted, linear or branched alkyl radical of 1 to 10 carbon atoms attached to the terminal nitrogen of a  $\text{-NHCONH-}$  radical. More preferred N'-alkylureido radicals are "lower N'-alkylureido" radicals in which the alkyl moiety has 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

25

An N'-alkylureido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an N'-alkylureido group are themselves unsubstituted.

30

Preferred optionally substituted N'-alkylureido radicals include N'-methyleureido, N'-ethyleureido, N'-n-propyleureido, N'-i-propyleureido, N'-n-butyleureido, N'-sec-butyleureido, N'-t-butyleureido, N'-trifluoromethyleureido, N'-difluoromethyleureido, N'-hydroxymethyleureido, N'-2-hydroxyethyleureido and N'-2-hydroxypropyleureido.

5

As used herein, the term N',N'-dialkylureido embraces radicals containing a radical -NHCON where the terminal nitrogen is attached to two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms. More preferred N',N'-dialkylureido radicals are "lower N',N'-dialkylureido" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

10

A N',N'-dialkylureido group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an N',N'-dialkylureido group are themselves unsubstituted.

15

Preferred optionally substituted N',N'-dialkylureido radicals include N',N'-dimethyleureido, N',N'-diethyleureido, N'-methyl,N'-ethyleureido, N',N'-di(n-propyl)ureido, N'-n-propyl,N'-methyleureido, N'-n-propyl,N'-ethyleureido, N',N'-di(i-propyl)ureido, N'-i-propyl,N'-methyleureido, N'-i-propyl,N'-ethyleureido, N',N'-di(n-butyl)ureido, N'-n-butyl,N'-methyleureido, N'-n-butyl,N'-ethyleureido, N'-n-butyl,N'-(i-propyl)ureido, N',N'-di(sec-butyl)ureido, N'-sec-butyl,N'-methyleureido, N'-sec-butyl,N'-ethyleureido, N'-sec-butyl,N'-(n-propyl)ureido, N'-sec-butyl,N'-(i-propyl)ureido, N',N'-di(t-butyl)ureido, N'-t-butyl,N'-methyleureido, N'-t-butyl,N'-ethyleureido, N'-t-butyl,N'-(n-propyl)ureido, N'-t-butyl,N'-(i-propyl)ureido, N'-trifluoromethyl,N'-methyleureido, N'-trifluoromethyl,N'-ethyleureido, N'-trifluoromethyl,N'-(n-propyl)ureido, N'-trifluoromethyl,N'-(i-propyl)ureido, N'-trifluoromethyl,N'-(n-butyl)ureido, N'-trifluoromethyl,N'-(sec-butyl)ureido, N'-difluoromethyl,N'-methyleureido, N'-difluoromethyl,N'-ethyleureido, N'-difluoromethyl,N'-(n-propyl)ureido, N'-difluoromethyl,N'-(i-propyl)ureido, N'-difluoromethyl,N'-(n-butyl)ureido, N'-difluoromethyl,N'-(sec-butyl)ureido, N'-difluoromethyl,N'-(t-butyl)ureido, N'-difluoromethyl,N'-trifluoromethyleureido, N'-hydroxymethyl,N'-methyleureido, N'-ethyl,N'-hydroxymethyleureido, N'-hydroxymethyl,N'-(n-propyl)ureido, N'-hydroxymethyl,N'-(i-propyl)ureido, N'-n-butyl,N'-hydroxymethyleureido, N'-sec-butyl,N'-hydroxymethyleureido, N'-t-butyl,N'-hydroxymethyleureido, N'-difluoromethyl,N'-hydroxymethyleureido, N'-

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hydroxymethyl,N'-trifluoromethylureido, N'-hydroxyethyl,N'-methylureido, N'-ethyl,N'-hydroxyethylureido, N'-hydroxyethyl,N'-(n-propyl)ureido, N'-hydroxyethyl,N'-(i-propyl)ureido, N'-(n-butyl),N'-hydroxyethylureido, N'(sec-butyl),N'-hydroxyethylureido, N'-(t-butyl),N'-hydroxyethylureido, N'-difluoromethyl,N'-hydroxyethylureido, N'-hydroxyethyl,N'-trifluoromethylureido, N'-hydroxypropyl,N'-methylureido, N'-ethyl,N'-hydroxypropylureido, N'-hydroxypropyl,N'-(n-propyl)ureido, N'-hydroxypropyl,N'-(i-propyl)ureido, N'-(n-butyl),N'-hydroxypropylureido, N'(sec-butyl),N'-hydroxypropylureido, N'(t-butyl),N'-hydroxypropylureido, N'-difluoromethyl,N'-hydroxypropylureido y N'-hydroxypropyl,N'-trifluoromethylureido.

10

As used herein, the term acyl embraces optionally substituted, linear or branched radicals having 2 to 20 carbon atoms or, preferably 2 to 12 carbon atoms attached to a carbonyl radical. More preferably acyl radicals are "lower acyl" radicals of formula -COR, wherein R is a hydrocarbon group, preferably an alkyl group, having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms.

15

An acyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on an acyl group are themselves unsubstituted.

20

Preferred optionally substituted acyl radicals include acetyl, propionyl, butyryl, isobutyryl, isovaleryl, pivaloyl, valeryl, lauryl, myristyl, stearyl and palmityl,

25

As used herein, the term aryl radical embraces typically a C<sub>5</sub>-C<sub>14</sub> monocyclic or polycyclic aryl radical such as phenyl, naphthyl, anthranyl and phenanthryl. Phenyl is preferred.

30

A said optionally substituted aryl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups, alkoxycarbonyl groups in which the alkyl moiety has from 1 to 4 carbon atoms, hydroxycarbonyl groups, carbamoyl groups, nitro groups, cyano groups, C<sub>1</sub>-C<sub>4</sub> alkyl groups, C<sub>1</sub>-C<sub>4</sub> alkoxy groups and C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl groups. When an aryl radical carries

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2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on an aryl group are typically themselves unsubstituted.

As used herein, the term heteroaryl radical embraces typically a 5- to 14-  
5 membered ring system, preferably a 5- to 10- membered ring system, comprising at least one heteroaromatic ring and containing at least one heteroatom selected from O, S and N. A heteroaryl radical may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom.

10 A said optionally substituted heteroaryl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine, chlorine or bromine atoms, alkoxy carbonyl groups in which the alkyl moiety has from 1 to 4 carbon atoms, nitro groups, hydroxy groups, C<sub>1</sub>-C<sub>4</sub> alkyl groups and C<sub>1</sub>-C<sub>4</sub> alkoxy groups. When  
15 an heteroaryl radical carries 2 or more substituents, the substituents may be the same or different. Unless otherwise specified, the substituents on a heteroaryl radical are typically themselves unsubstituted.

Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furyl, benzofuranyl,  
20 oxadiazolyl, oxazolyl, isoxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, thiadiazolyl, thienyl, pyrrolyl, pyridinyl, benzothiazolyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, quinoliziny, cinnolinyl, triazolyl, indoliziny, indoliny, isoindoliny, isoindolyl, imidazolidinyl, pteridinyl, thianthrenyl, pyrazolyl, 2H-pyrazolo[3,4-d]pyrimidinyl, 1H-pyrazolo[3,4-d]pyrimidinyl, thieno[2,3-d]  
25 pyrimidinyl and the various pyrrolopyridyl radicals.

Oxadiazolyl, oxazolyl, pyridyl, pyrrolyl, imidazolyl, thiazolyl, thiadiazolyl, thienyl, furanyl, quinoliny, isoquinoliny, indolyl, benzoxazolyl, naphthyridinyl, benzofuranyl, pyrazinyl, pyrimidinyl and the various pyrrolopyridyl radicals are preferred.

30 As used herein, the term cycloalkyl embraces saturated carbocyclic radicals and, unless otherwise specified, a cycloalkyl radical typically has from 3 to 7 carbon atoms.

A cycloalkyl radical is typically unsubstituted or substituted with 1, 2 or 3  
35 substituents which may be the same or different. The substituents are preferably selected

from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. When a cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different. Typically the substituents on a cycloalkyl group are themselves unsubstituted. The cycloalkyl radicals of the present invention also

5 comprise monocyclic C<sub>3-7</sub> carbon rings fused with a phenyl ring.

Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, tetrahydrobenzanulene, tetrahydronaphthyl, bicyclo[4.2.0]octa-1,3,5-triene and indanyl. It is preferably cyclopropyl, cyclopentyl, indanyl and cyclohexyl.

10

As used herein, the term cycloalkenyl embraces partially unsaturated carbocyclic radicals and, unless otherwise specified, a cycloalkenyl radical typically has from 3 to 7 carbon atoms.

15

A cycloalkenyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. When a cycloalkenyl radical carries 2 or more substituents, the substituents may be the same or different. Typically, the substituents on a cycloalkenyl

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group are themselves unsubstituted.

Examples include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. Cyclopentenyl and cyclohexenyl are preferred.

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As used herein, the term heterocyclyl radical embraces typically a non-aromatic, saturated or unsaturated C<sub>3</sub>-C<sub>10</sub> carbocyclic ring system, such as a 5, 6 or 7 membered radical, in which one or more, for example 1, 2, 3 or 4 of the carbon atoms preferably 1 or 2 of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl radicals are preferred. A heterocyclic radical may be a single ring or two or

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more fused rings wherein at least one ring contains a heteroatom. When a heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

A said optionally substituted heterocyclyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The

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substituents are preferably selected from halogen atoms, preferably fluorine atoms,

hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, the substituents on a heterocyclyl radical are themselves unsubstituted.

Examples of heterocyclic radicals include piperidyl, pyrrolidyl, pyrrolinyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrazolinyl, pirazolidinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl, cromanyl, isocromanyl, imidazolidinyl, imidazolyl, oxiranyl, azaridinyl, 4,5-dihydro-oxazolyl, 2-benzofuran-1(3H)-one, 1,3-dioxol-2-one and 3-azatetrahydrofuranlyl.

Where a heterocyclyl radical carries 2 or more substituents, the substituents may be the same or different.

As used herein, some of the atoms, radicals, moieties, chains and cycles present in the general structures of the invention are "optionally substituted". This means that these atoms, radicals, moieties, chains and cycles can be either unsubstituted or substituted in any position by one or more, for example 1, 2, 3 or 4, substituents, whereby the hydrogen atoms bound to the unsubstituted atoms, radicals, moieties, chains and cycles are replaced by chemically acceptable atoms, radicals, moieties, chains and cycles. When two or more substituents are present, each substituent may be the same or different. The substituents are typically themselves unsubstituted.

Typically when a cyclic radical is bridged by an alkylene or alkylenedioxy radical, the bridging alkylene radical is attached to the ring at non-adjacent atoms.

As used herein, the term halogen atom embraces chlorine, fluorine, bromine and iodine atoms. A halogen atom is typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

As used herein, an acylamino group is typically a said acyl group attached to an amino group.

As used herein an alkylenedioxy group is typically -O-R-O-, wherein R is a said alkylene group.

As used herein, an alkoxycarbonyl group is typically a said alkoxy group attached to a said carbonyl group.

As used herein, an acyloxy group is typically a said acyl group attached to an  
5 oxygen atom.

As used herein, a cycloalkoxy group is typically a said cycloalkyl group attached to an oxygen atom.

10 Compounds containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include  
15 both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and  
20 alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

As used herein, an N-oxide is formed from the tertiary basic amines or imines present in the molecule, using a convenient oxidising agent.

25

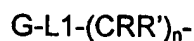
According to one embodiment of the present invention in the compounds of formula (I)  $R^1$  is selected from the group consisting of hydrogen atoms and lower alkyl groups, which are optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, alkylthio, hydroxycarbonyl and alkoxycarbonyl  
30 groups.

According to another embodiment of the present invention in the compounds of formula (I)  $R^2$  is a heteroaryl group which is optionally substituted by one or more substituents selected from halogen atoms and alkyl, hydroxy, hydroxyalkyl,  
35 hydroxycarbonyl, alkoxy, alkylenedioxy, alkoxycarbonyl, aryloxy, acyl, acyloxy, alkylthio,

arylthio, amino, nitro, cyano, mono- or di-alkylamino, acylamino, carbamoyl or mono- or di-alkylcarbamoyl, difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups.

5 According to another embodiment of the present invention in the compounds of formula (I)  $R^2$  is a N-containing heteroaryl group. It is also preferred that  $R^2$  is optionally substituted by one or more substituents selected from halogen atoms and lower alkyl groups

10 According to still another embodiment of the present invention in the compounds of formula (I)  $R^4$  represents:



wherein

15

$n$  is an integer from 1 to 3

$R$  and  $R'$  are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

$L1$  is a linker selected from the group consisting of a direct bond,  $-O-$ ,  $-O(CO)-$ ,  $-(CO)O-$  and  $-O(CO)O-$  groups

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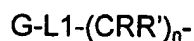
$G$  is selected from alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups said groups being optionally substituted with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more
- 25 substituents selected from halogen atoms; and
- hydroxy, alkoxy, cyano and cycloalkyloxy groups,

It is particularly advantageous that when  $n$  is zero,  $L1$  is a direct bond and  $G$  is different from a hydrogen atom.

30

It is still a further preferred embodiment of the present invention that in the compounds of formula (I)  $R^4$  represents:



35 wherein

n is an integer from 1 to 3

R and R' are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

L1 is a linker selected from the group consisting of a direct bond, -O-, -O(CO)- and -

5 O(CO)O- groups

G is selected from alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups said groups being optionally substituted with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more
- 10 substituents selected from halogen atoms; and
- hydroxy, alkoxy and cycloalkyloxy groups,

According to still another embodiment of the present invention in the compounds of formula (I) R<sup>4</sup> represents:

15 
$$G-L1-(CRR')_n-$$

wherein

n is an integer from 1 to 2

20 R and R' are independently selected from the group consisting of hydrogen atoms and methyl groups

L1 is selected from direct bond and groups -O-, -(CO)O- and -O(CO)O-; and

G is selected from alkyl, cycloalkyl, aryl and heteroaryl groups said groups being optionally substituted with one or more halogen atoms or groups alkoxy, cyano, alkyl or -CF<sub>3</sub>;

25

It is still a further preferred embodiment of the present invention that in the compounds of formula (I) R<sup>4</sup> represents:

30 
$$G-L1-(CRR')_n-$$

wherein

n is an integer from 1 to 2

R and R' are independently selected from the group consisting of hydrogen atoms and methyl groups

35 L1 is a direct bond; and

G is selected from alkyl, cycloalkyl, aryl and heteroaryl groups said groups being optionally substituted with one or more halogen atoms;

According to another embodiment of the present invention in the compounds of  
5 formula (I) R<sup>3</sup> represents a hydrogen atom or an acyl group

Particular individual compounds of the invention include:

- 10 ethyl 4-acetyl-1-ethyl-6-oxo-5-(quinolin-5-ylamino)-1,6-dihydropyridazine-3-carboxylate
- ethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- ethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 ethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- isopropyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 20 benzyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- isopropyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-methylbutyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 25 2-methoxyethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- cyclopropylmethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 30 methyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 2-phenylethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- benzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- cyclohexyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
tert-butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 cyclobutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
cyclohexyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate  
1-methyl-2-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 10 1-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
tert-butyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 1-phenylethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate  
sec-butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
2-(dimethylamino)-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 20 2-methoxy-1-methyl-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
benzyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 ethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate  
ethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate  
isopropyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 30 pyridin-2-ylmethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate  
isopropyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate  
ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- isopropyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-thienylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 3-thienylmethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 10 3-methoxybenzyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 1-phenylethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-pyridin-4-ylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 20 1-pyridin-4-ylethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-pyridin-4-ylethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 2,3-dihydro-1H-inden-1-yl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 2,3-dihydro-1H-inden-1-yl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1,3,3-Trimethylbutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Chlorobenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 3-Methoxybenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- Benzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- Octyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1,5-Dimethylhex-4-en-1-yl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 Allyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- Benzoyloxycarbonylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2-Oxo-2-phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 10 Dimethylcarbamoylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2-Phenoxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 2-Dimethylaminoethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Bromobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Bromobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 20 4-Bromobenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 2-Chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 2-Chlorobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Methylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Trifluoromethylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 3-Trifluoromethylbenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Trifluoromethylbenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate

- 2-(Benzylmethylamino)-ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 3-Cyanobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Cyanobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 10 Cyclohexyloxycarbonyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-Cyclohexyloxycarbonyloxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2,2-Dimethylbutyryloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 (S)-2-Amino-4-methylpentanoyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

and pharmaceutically acceptable salts thereof.

- 20 Of outstanding interest are:

- benzyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- pyridin-2-ylmethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 25 ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-thienylmethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 3-chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- 2,3-dihydro-1H-inden-1-yl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
ethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
5 benzyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate  
isopropyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
benzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
10 cyclobutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
  
1-methyl-2-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
15 1-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
1-phenylethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate  
20 2-Phenoxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
4-Bromobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
3-Methylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
25 4-Methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
3-Cyanobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
30 Cyclohexyloxycarbonyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate  
2,2-Dimethylbutyryloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

35 and pharmaceutically acceptable salts thereof.

According to another embodiment the present invention covers pharmaceutical compositions comprising one or more of the compounds of formula (I), as hereinabove described, in admixture with pharmaceutically acceptable diluents or carriers.

5

In still another embodiment the present invention covers a combination product comprising (i) a compound of formula (I), as hereinabove described, and (ii) another compound selected from (a) steroids, (b) immunosuppressive agents, (c) T-cell receptor blockers, (d) antiinflammatory drugs, (e)  $\beta$ 2-adrenergic agonists and (f) antagonists of M3 muscarinic receptors; for simultaneous, separate or sequential use in the treatment of the human or animal body.

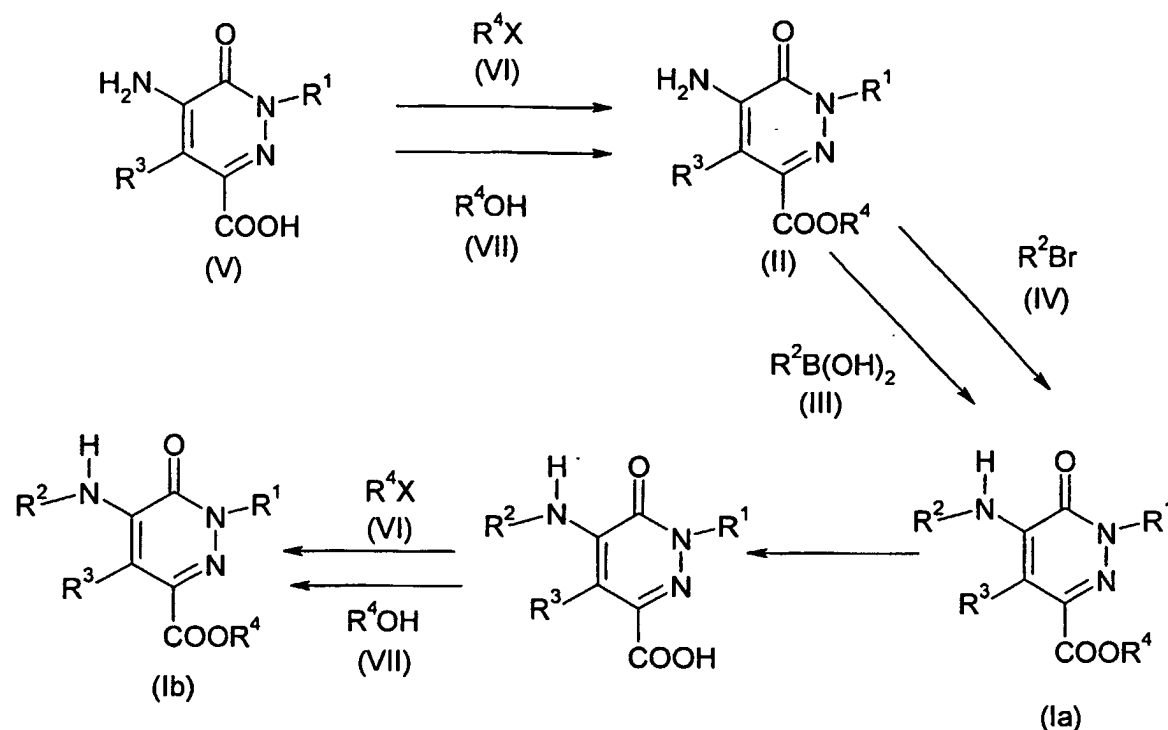
According to still another embodiment of the present invention is directed to the use of a compound of formula (I), as hereinabove described, in the manufacture of a medicament for the treatment or prevention of a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4. It is a preferred embodiment to use the compound of formula (I) in the manufacture of a medicament for use in the treatment or prevention of a disorder which is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

According to still another embodiment the present invention covers a method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4, which method comprises administering to the said subject an effective amount of a compound of formula (I), as hereinabove described. In a preferred embodiment the method is used for treating a subject afflicted with a pathological condition or disease which is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

The compounds of the present invention may be prepared by one of the processes described below.

Compounds (I) may be obtained as shown in Scheme 1.

Scheme 1



4-Aminopyridazin-3(2H)-one derivatives of formula (V), wherein  $R^1$  and  $R^3$  are as hereinbefore defined, are reacted with an alkylating agent of formula (VI), wherein  $R^4$  is as hereinbefore defined and X is a leaving group such as a chlorine or a bromine atom, in an aprotic solvent in the presence of a base by methods known per se, e. g. D. A. White. *Synthetic Communications*, 1977, 7(8), 559-568, to give compounds of formula (II), wherein  $R^1$ ,  $R^3$  and  $R^4$  are as hereinbefore defined.

Alternatively, 4-aminopyridazin-3(2H)-one derivatives of formula (V), wherein  $R^1$  and  $R^3$  are as hereinbefore defined, are condensed with an alcohol of formula (VII) wherein  $R^4$  is as hereinbefore described in the presence of triphenylphosphine and diethyl azodicarboxylate by methods known per se, e. g. O. Mitsunobu. *Synthesis*, 1981, 1, 1-28, to give compounds of formula (II), wherein  $R^1$ ,  $R^3$  and  $R^4$  are as hereinbefore defined.

Condensation of 4-aminopyridazin-3(2H)-one derivatives (II), wherein  $R^1$ ,  $R^3$ , and  $R^4$  are as hereinbefore defined, with a boronic acid of formula (III), wherein  $R^2$  is as hereinbefore defined, gives compounds of formula (Ia), wherein  $R^1$ ,  $R^2$ ,  $R^3$ , and  $R^4$  are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as

cupric acetate and an organic base, preferably an amine base such as triethylamine, in an inert solvent such as dioxane, methylene chloride or tetrahydrofuran, at a temperature from -20° C to the boiling point of the solvent.

5           Alternatively, condensation of 4-aminopyridazin-3(2H)-ones (II) with an heteroaryl bromide of formula (IV) wherein R<sup>2</sup> is as hereinbefore defined, gives compounds (Ia), wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are as hereinbefore defined. The reaction is carried out in the presence of a copper salt such as cuprous iodide and an inorganic base such as potassium phosphate, potassium carbonate or sodium carbonate and can also be  
10 performed in the presence of an organic base, preferably a diamine base such as N, N'-dimethylethylenediamine in an inert solvent such as toluene, dioxane or dimethylformamide, at a temperature from -20°C to the boiling point of the solvent. It can also be performed neat.

15

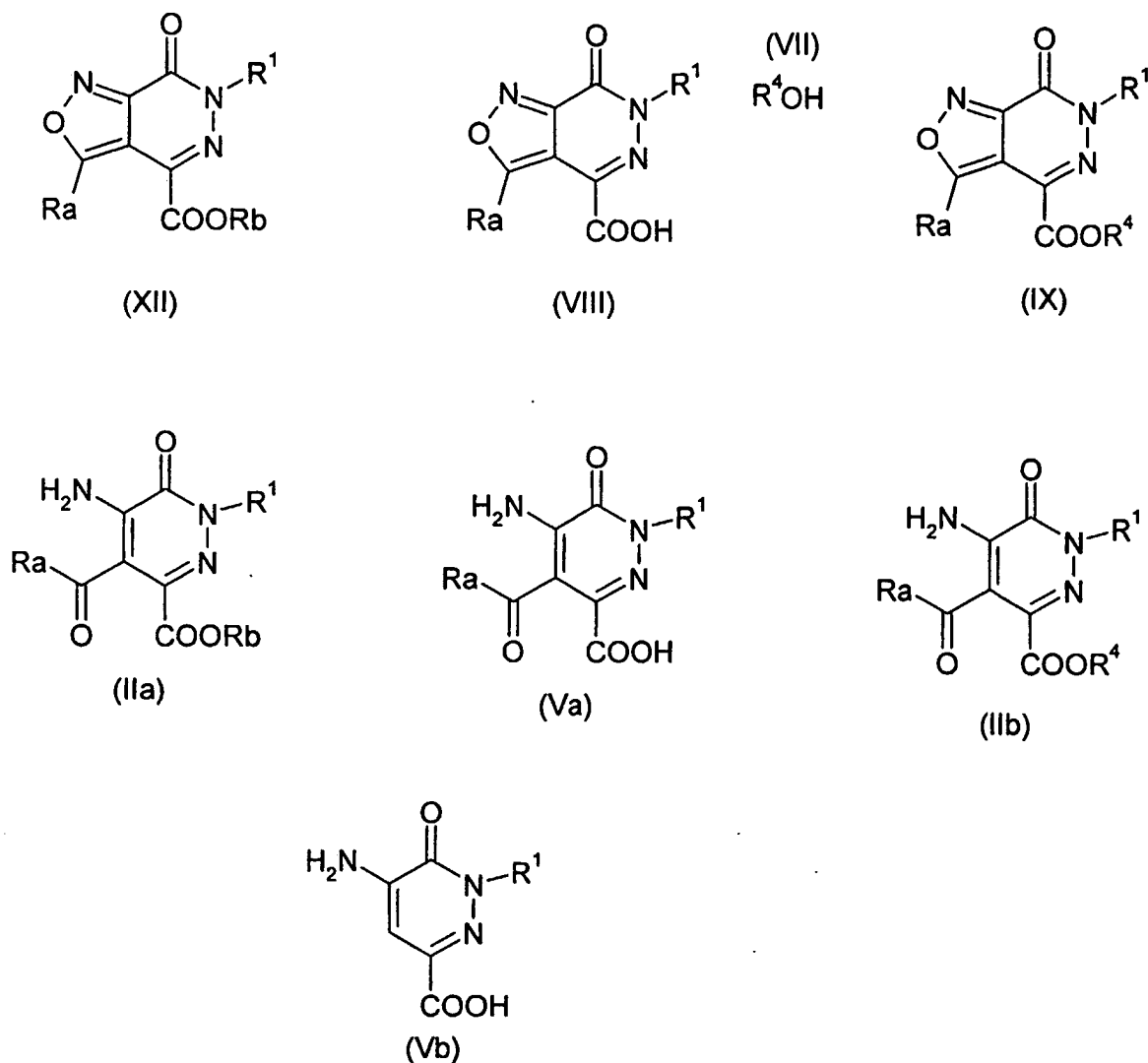
Compound (Ia) may be optionally hydrolysed with a suitable base to yield an acid intermediate. This intermediate is then alkylated using an alkylating agent of formula (VI), where R<sup>4</sup> has been previously defined and X is a leaving group such as a bromine or a chlorine atom, in an aprotic solvent in the presence of a base using known methods, for  
20 example D.A. White *Synthetic Communications*, 1977, 7(8), 559-568, giving compounds of formula (Ib), where R<sup>1</sup>, R<sup>3</sup> and R<sup>4</sup> have been previously defined.

As an alternative these intermediate acids, can also be converted to (Ib) by condensation with an alcohol of formula (VII) in the presence of triphenylphosphine and  
25 diethyl azodicarboxylate using known methods, for example O. Mitsunobu *Synthesis*, 1981, 1, 1-28.

Pyridazin-3(2H)-ones of formula (V) in particular those of formula (Va) where R<sup>3</sup> is a group Ra-CO- wherein Ra represents an alkylcarbonyl group wherein the  
30 alkyl group may be substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl groups and those of formula (Vb) wherein R<sup>3</sup> is a hydrogen atom, may be obtained as shown in Scheme 2.

35

## Scheme 2



Isoxazolo[3,4-d]pyridazin-7(6H)-ones of formula (XII), wherein  $R^1$  and  $R_a$  are as hereinbefore defined and  $R_b$  is a short chain alkyl rest, are hydrogenated to yield 4-aminopyridazin-3(2H)-one derivatives (IIa), wherein  $R^1$ ,  $R_a$  and  $R_b$  are as hereinbefore defined. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known per se, e. g. V. Dal Piaz et al. *Heterocycles*, **1991**, 32, 1173.

Alternatively, isoxazolo[3,4-d]pyridazin-7(6H)-ones of formula (XII), wherein  $R^1$ ,  $R_a$  and  $R_b$  are as hereinbefore defined are hydrolysed with sodium or potassium hydroxide and the resulting product is subsequently neutralised with an inorganic acid such as hydrochloric or sulphuric acid to give the corresponding carboxylic acid derivatives of

formula (VIII), wherein  $R^1$  and  $R_a$  are as hereinbefore defined. The reaction is preferably carried out in a solvent such as methanol, ethanol, tetrahydrofuran or an aqueous mixture of one of the above mentioned solvents at its boiling point.

5 Isoxazole derivatives of formula (VIII), wherein  $R^1$  and  $R_a$  are as hereinbefore defined, are condensed with an alcohol of formula (VII) wherein  $R^4$  is as hereinbefore defined, according the method above described, (O. Mitsunobu. *Synthesis*, **1981**, 1, 1-28) to give compounds of formula (IX), wherein  $R^1$ ,  $R_a$  and  $R^4$  are as hereinbefore defined.

10 Isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (IX), wherein  $R^1$ ,  $R_a$  and  $R^4$  are as hereinbefore defined, are hydrogenated to yield 4-aminopyridazin-3(2*H*)-one derivatives (IIb), wherein  $R^1$ ,  $R_a$  and  $R^4$  are as hereinbefore defined. The hydrogenation may be performed using for example hydrogen in the presence of a catalyst by methods known per se, e. g. V. Dal Piaz et al. *Heterocycles*, **1991**, 32, 1173.

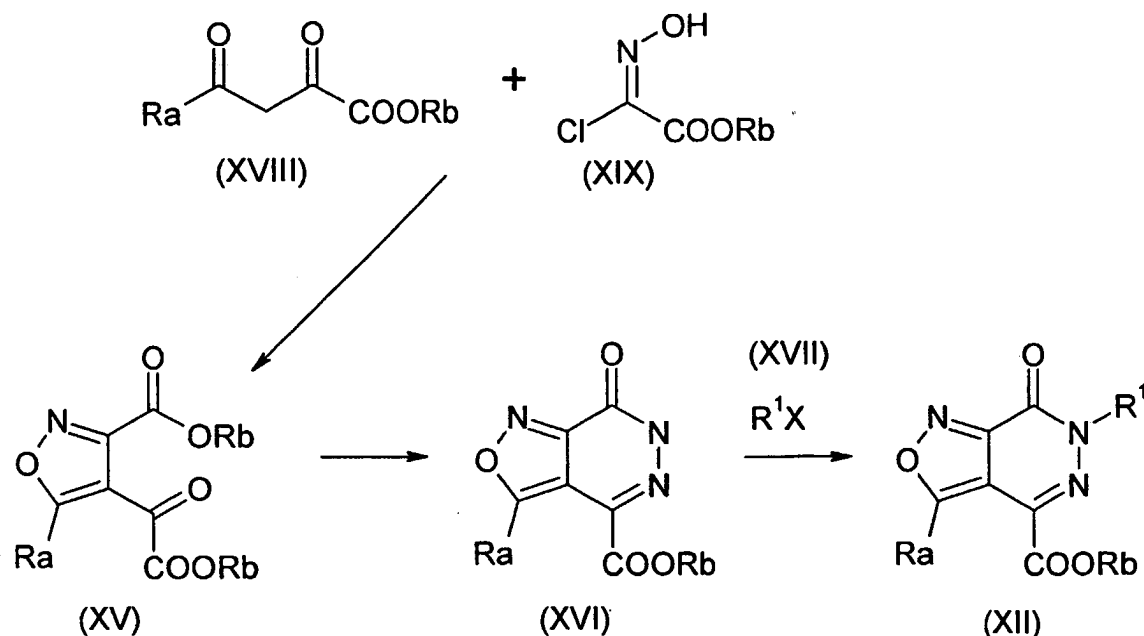
15

Hydrolysis of 4-aminopyridazin-3(2*H*)-one derivatives (IIb), wherein  $R^1$ ,  $R_a$  and  $R^4$  are as hereinbefore defined, with sodium or potassium hydroxide and subsequent neutralisation with an inorganic acid such as hydrochloric or sulphuric acid provides the corresponding carboxylic acid derivatives of formula (Va), wherein  $R^1$  and  $R_a$  are as  
20 hereinbefore defined. The reaction is preferably carried out in a solvent such as methanol, ethanol, tetrahydrofuran or an aqueous mixture of one of the above mentioned solvents at its boiling point. The same procedure may be followed to hydrolyse the compounds of formula (IIa).

25 Treatment of 4-aminopyridazin-3(2*H*)-one derivatives (IIa), wherein  $R^1$ ,  $R_a$  and  $R_b$  are as hereinbefore defined, or the carboxylic acid derivatives (Va), wherein  $R^1$  and  $R_a$  are as hereinbefore defined, with hydrobromic acid at reflux, gives compounds (Vb), wherein  $R^1$  is as hereinbefore defined.

30 Isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones of formula (XII) may be obtained as shown in Scheme 3.

## Scheme 3



Reaction of a 2,4-dioxoester derivative of general formula (XVIII), wherein Ra and Rb are as hereinbefore defined, and a 2-chloro-2-(hydroxyimino)acetate derivative of formula (XIX), wherein Rb is as hereinbefore defined, following methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, 95, 1478, gives isoxazole derivatives of formula (XV), wherein Ra and Rb are as hereinbefore defined.

Isoxazole derivatives of formula (XV), wherein Ra and Rb are hereinbefore defined, are condensed with hydrazine, by methods known per se, e. g. G. Renzi et al., *Gazz. Chim. Ital.* **1965**, 95, 1478, to give isoxazolo[3,4-d]pyridazin-7(6H)-ones of formula (XVI) wherein Ra and Rb are as hereinbefore defined. Subsequent reaction with an alkylating agent of formula (XVII), wherein R<sup>1</sup> is as hereinbefore defined and X is a leaving group such as a chlorine or a bromine atom or a methanesulfonate, p-toluenesulfonate or a benzenesulfonate group, by methods known per se, e. g. V. Dal Piaz et al. *Drug Des. Discovery* **1996**, 14, 53; or condensation with an alcohol of formula (XVII) wherein R<sup>1</sup> is as hereinbefore described and X is a hydroxy group in the presence of triphenylphosphine and diethyl azodicarboxylate by methods known per se, e. g. O. Mitsunobu et al. *J. Am. Chem. Soc.* **1972**, 94, 679; gives isoxazolo[3,4-d]pyridazin-7(6H)-ones of formula (XII), wherein R<sup>1</sup>, Ra and Rb are as hereinbefore defined.

When the defined groups R<sup>1</sup> to R<sup>4</sup> are susceptible to chemical reaction under the conditions of the hereinbefore described processes or are incompatible with said processes, conventional protecting groups may be used in accordance with standard practice, for example see T. W. Greene and P. G. M. Wuts in 'Protective Groups in Organic Chemistry', 3<sup>rd</sup> Edition, John Wiley & Sons (1999). It may be that deprotection will form the last step in the synthesis of compounds of formula (I).

The compounds of formulae (III), (IV), (VI), (VII), (XVII), (XVIII) and (XIX) are known compounds or can be prepared by analogy with known methods.

## PHARMACOLOGICAL ACTIVITY

### **PDE4 Assay Procedure**

Compounds to be tested were resuspended in DMSO at a stock concentration of 1 mM. The compounds were tested at different concentrations varying from 10 pM to 10  $\mu$ M to calculate an IC<sub>50</sub>. These dilutions were done in 96-well plates. In some cases, plates containing diluted compounds were frozen before being assayed. In these cases, the plates were thawed at room temperature and stirred for 15 minutes.

Ten microliters of the diluted compounds were poured into a "low binding" assay plate. Eighty microliters of reaction mixture containing 50 mM Tris pH 7.5, 8.3 mM MgCl<sub>2</sub>, 1.7 mM EGTA, and 15 nM [3H]-cAMP were added to each well. The reaction was initiated by adding ten microliters of a solution containing PDE4. The plate was then incubated under stirring for 1 hour at room temperature. After incubation the reaction was stopped with 50 microlitres of SPA beads, and the reaction was allowed to incubate for another 20 minutes at room temperature before measuring radioactivity using standard instrumentation.

The reaction mixture was prepared by adding 90 ml of H<sub>2</sub>O to 10 ml of 10X assay buffer (500 mM Tris pH 7.5, 83 mM MgCl<sub>2</sub>, 17 mM EGTA), and 40 microlitres 1  $\mu$ Ci/ $\mu$ L [3H]-cAMP. SPA beads solution was prepared by adding 500 mg to 28 ml H<sub>2</sub>O for a final concentration of 20 mg/ml beads and 18 mM zinc sulphate.

The results are shown in Table 1.

No	HPDE4B or IC <sub>50</sub> PDE4 (nM)
1	52
5	110
7	10
10	19
11	1,6
13	2,9
14	2,4
19	9,8
23	14
26	5,1
27	16
33	1,9
36	44
38	13
39	1,5
41	69
49	0,73
51	0,48
66	0,36
69	0,49
71	5,0

It can be seen from Table 1 that the compounds of formula (I) are potent inhibitors of phosphodiesterase 4 (PDE 4). Preferred pyridazin-3(2*H*)-one derivatives of the invention possess an IC<sub>50</sub> value for the inhibition of PDE4 (determined as defined above) of less than 120 nM, preferably less than 50 nM and most preferably less than 30 nM. The compounds are also capable of blocking the production of some pro-inflammatory cytokines such as, for example, TNF $\alpha$ .

Thus, they can be used in the treatment of allergic, inflammatory and immunological diseases, as well as those diseases or conditions where the blockade of pro-inflammatory cytokines or the selective inhibition of PDE 4 could be of benefit. These disease states include asthma, chronic obstructive pulmonary disease, allergic rhinitis, rheumatoid arthritis, osteoarthritis, osteoporosis, bone-formation disorders, glomerulonephritis, multiple sclerosis, ankylosing spondylitis, Graves opthalmopathy, myasthenia gravis, diabetes insipidus, graft rejection, gastrointestinal disorders such as irritable bowel disease, ulcerative colitis or Crohn disease, septic shock, adult distress respiratory syndrome, and skin diseases such as atopic dermatitis, contact dermatitis, acute dermatomyositis and psoriasis. They can also be used as improvers of cerebrovascular function as well as in the treatment of other CNS related diseases such as dementia, Alzheimer's disease, depression, and as nootropic agents.

#### Plasma stability assay

For plasma stability assays, compounds in acetonitrile or dimethylsulfoxide solutions are added in duplicate to 1 mL plasma pre-warmed at 37°C at a final concentration of 1 µg/mL (less than 1 % organic solvent added). Just after the addition of the compounds and mixing (t= 0h), 100 µL samples are collected and transferred to tubes containing 300 µL of 0.5% trifluoro acetic acid in acetonitrile in an ice bath in order to stop the reaction. Samples are kept in a water bath at 37°C during the assay. At different time intervals (i.e. t= 0.5, 1, 3 and 24h) samples are collected and reaction stopped as described previously. The aliquots are centrifuged at 4000 rpm for 10 minutes, 100 µL of supernatant diluted with 100 µL Milli-Q water and 5 µL injected in a HPLC/MS system. Both the parent compound and the possible by-products are monitored. The stability is calculated by comparing the compound response obtained at a given time with the response at time = 0 h.

The compounds of the present invention show a short half life in plasma, which is preferably shorter than 5 hours, more preferably shorter than 3 hours and most preferably shorter than 1 hour. The free acid derivatives originating from the hydrolysis of the group  $-COOR^4$  of the compounds of the present invention have an  $IC_{50}$  value for the inhibition of PDE4 which is several times higher than the  $IC_{50}$  value of the non-hydrolysed compounds.

Consequently the pyridazin-3(2*H*)-one derivative of the invention can be administered to a subject in need thereof at relatively high doses without causing undesirable systemic effects as a result of both their short half lives in plasma and the reduced PDE4 inhibition capacity of the their hydrolisates.

5

The compounds of the present invention are also of benefit when administered in combination with other drugs such as steroids and immunosuppressive agents, such as cyclosporin A, rapamycin, T-cell receptor blockers,  $\beta$ 2-adrenergic agonists or antagonists of M3 muscarinic receptors. In this case the administration of the compounds allows a  
10 reduction of the dosage of the other drugs, thus preventing the appearance of the undesired side effects associated with both steroids and immunosuppressants.

Like other PDE4 inhibitors (see references above) the compounds of the invention can also be used for blocking, after preventive and/or curative treatment, the  
15 erosive and ulcerogenic effects induced by a variety of etiological agents, such as antiinflammatory drugs (steroidal or non-steroidal antiinflammatory agents), stress, ammonia, ethanol and concentrated acids.

They can be used alone or in combination with antacids and/or antisecretory  
20 drugs in the preventive and/or curative treatment of gastrointestinal pathologies like drug-induced ulcers, peptic ulcers, H. Pylori-related ulcers, esophagitis and gastro-esophageal reflux disease.

They can also be used in the treatment of pathological situations where damage  
25 to the cells or tissues is produced through conditions like anoxia or the production of an excess of free radicals. Examples of such beneficial effects are the protection of cardiac tissue after coronary artery occlusion or the prolongation of cell and tissue viability when the compounds of the invention are added to preserving solutions intended for storage of transplant organs or fluids such as blood or sperm. They are also of benefit on tissue  
30 repair and wound healing.

Accordingly, the pyridazin-3(2*H*)-one derivatives of the invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compound and/or salts thereof, may be used in a method of treatment or prevention  
35 of disorders of the human body susceptible to amelioration by inhibition of

phosphodiesterase 4 which comprises administering to a patient requiring such treatment an effective amount of a pyridazin-3(2*H*)-one derivative of the invention.

The results of table I show that the compounds of formula (I) are potent inhibitors of phosphodiesterase 4 (PDE4) and are therefore useful in the treatment or prevention of pathological conditions, diseases and disorders known to be susceptible of amelioration by inhibition of PDE4, such as asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

The compounds of the present invention can also be used in combination with other drugs known to be effective in the treatment of these diseases. For example, in combination with steroids, immunosuppressive agents, T-cell receptor blockers, antiinflammatory drugs  $\beta$ 2-adrenergic agonists and/or antagonists of M3 muscarinic receptors for simultaneous, separate or sequential use in the treatment of the human or animal body

Accordingly, another embodiment of the invention is the use of the compounds of formula (I) in the manufacture of a medicament for treatment or prevention of pathological conditions, diseases and disorders known to be susceptible of amelioration by inhibition of PDE4, as well as a method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of PDE4, which comprises administering to said subject an effective amount of a compound of formula (I).

The present invention also provides pharmaceutical compositions which comprise, as an active ingredient, at least a pyridazin-3(2*H*)-one derivative of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight, of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application. Preferably the compositions are made up in a form suitable for oral, topical, nasal, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such compound, to form the compositions of this invention are well-

known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

Compositions for oral administration may take the form of tablets, retard tablets, sublingual tablets, capsules, inhalation aerosols, inhalation solutions, dry powder inhalation, or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

Compositions for topical administration may take the form of ointments, creams or lotions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples (including Preparation Examples 1 to 50) which do not limit the scope of the invention in any way.

5 <sup>1</sup>H Nuclear Magnetic Resonance Spectra were recorded on a Varian Gemini 300 spectrometer.

Low Resolution Mass Spectra (m/z) were recorded on a Micromass ZMD mass spectrometer using ESI ionization.

10

Melting points were recorded using a Perkin Elmer DSC-7 apparatus.

The chromatographic separations were obtained using a Waters 2690 system equipped with a Symmetry C18 (2.1 x 10 mm, 3.5 mM) column. The mobile phase was  
15 formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL) and acetonitrile (500 mL) (B) and formic acid (0.46 mL), ammonia (0.115 mL) and water (1000 mL) (A): initially from 0% to 95% of B in 20 min, and then 4 min. with 95% of B. The reequilibration time between two injections was 5 min. The flow rate was 0.4 mL/min. The injection volume was 5  
20 microliter. Diode array chromatograms were collected at 210 nm.

20

## PREPARATION EXAMPLES

### PREPARATION 1

#### 25 **Ethyl 4-[ethoxy(oxo)acetyl]-5-methylisoxazole-3-carboxylate**

To an ice-cooled solution of sodium ethoxide (12.92 g, 0.19 mol) in 160 mL of dry ethanol ethyl 2,4-dioxovalerate (25.0 g, 0.158 mol) was added dropwise and the mixture was stirred at 0 °C for 30 min. A solution of ethyl chloro(hydroximino) acetate (28.79g, 0.190 mol) in 50 mL of dry ethanol was added dropwise. Then it was stirred at 0°C for 30  
30 min and at room temperature for 19 hours. Finally solvent was removed and the crude thus obtained was partitioned between ethyl acetate and water. The organic phase was dried and solvent removed to yield the desired product (100%) as an orange oil.

$\delta$  (CDCl<sub>3</sub>): 1.40 (m, 6H), 2.70 (s, 3H), 4.40 (m, 4H).

## PREPARATION 2

### **Ethyl 3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate**

Hydrazine monohydrate (8.7 mL, 180 mmol) was added dropwise to a solution of the title compound of Preparation 1 (38.3 g, 150 mmol) in dry ethanol (75 mL) and the resulting mixture was stirred overnight. After cooling with an ice bath, a precipitate was formed which was collected by filtration and washed with diethyl ether to yield the title compound (19.2 g, 57% yield) as a yellow solid.

$\delta$  (CDCl<sub>3</sub>): 1.41 (t, 3H), 3.01 (s, 3H), 4.50 (q, 2H), 6.30 (s, 1H).

## PREPARATION 3

### **Ethyl 6-ethyl-3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate**

To a suspension of the title compound of Preparation 2 (10.0 g, 44 mmol) and anhydrous potassium carbonate (30 g, 220 mmol) in dry dimethylformamide (50 mL) was added ethyl bromide (19.6 mL, 264 mmol) and the resulting mixture stirred at r.t. overnight. The mixture was concentrated and the residue thus obtained was suspended in dichloromethane, washed with water and brine, dried and concentrated to yield the title compound (9.72 g, 88% yield) as a yellow solid.

$\delta$  (CDCl<sub>3</sub>): 1.42 (m, 6H), 3.00 (s, 3H), 4.25 (q, 2H), 4.48 (q, 2H)

## PREPARATION 4

### **Ethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 3 (1.0g, 4 mmol) and 10% palladium on charcoal (200 mg) in ethanol (100 mL) was shaken under hydrogen at room temperature and 30 psi for 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure to yield the title compound (950 mg, 98% yield).

$\delta$  (CDCl<sub>3</sub>): 1.38 (m, 6H), 2.30 (s, 3H), 4.22 (q, 2H), 4.42 (q, 2H), 7.50 (bs, 2H).

## PREPARATION 5

### **5-Amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid**

A mixture of the title compound of Preparation 4 (0.25 g, 0.99 mmol) and 48% bromhydric acid (2 mL) is heated to 130 °C for 3h. Very slowly, this reaction mixture is

neutralized at room temperature with 8N NaOH and finally with solid potassium carbonate. Once the solvent is eliminated under reduced pressure, the residue is treated with boiling ethanol and filtered. This organic phase is evaporated and 0.17g of the final product are obtained. Yield = 94%.

- 5             $\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.2$  Hz, 3 H) 4.1 (q,  $J=7.1$  Hz, 2 H) 6.7 (s, 2 H) 6.8 (s, 1 H)  
13.1 (s, 1 H)

#### PREPARATION 6

##### 10    **Benzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (1.00 g, 5.46 mmol), benzyl bromide (1.94 mL, 16.4 mmol) and potassium carbonate (0.76g, 5.46 mmol) in dimethylformamide (25 mL) is heated at 80 °C for 24h. Once the solvent is evaporated under reduced pressure, the residue is suspended in water and extracted twice with  
15 chloroform. The organic phase is washed with water and brine, dried over magnesium sulphate, filtered and evaporated. The purification through a flash chromatography column (3:1 hexane/ethyl acetate to 1:1 as eluent) yields 0.85g of the desired final compound. Yield= 57%

- 20             $\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.1$  Hz, 3 H) 4.3 (q,  $J=7.2$  Hz, 2 H) 5.0 (s, 2 H) 5.4 (s, 2 H) 6.9  
(s, 1 H) 7.4 (m, 5 H)

#### PREPARATION 7

##### **Ethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

- 25            A mixture of the title compound of Preparation 5 (1.00 g, 5.46 mmol), ethyl bromide (1.51 mL, 16.4 mmol) and potassium carbonate (0.76g, 5.46 mmol) in dimethylformamide (30 mL) is heated at 50°C for 24h. The solvent is evaporated under reduced pressure and the residue is suspended in water and extracted twice with chloroform. The organic phase is washed with water and brine, dried with magnesium sulphate, filtered and the solvent  
30 evaporated under reduced pressure. After purification of the residue through a flash chromatography column, eluting with 2:1 hexane/ethyl acetate, 0.86g of the desired final compound are isolated. Yield= 74%

- $\delta$  (CDCl<sub>3</sub>) : 1.4 (m, 6 H) 4.3 (q,  $J=7.4$  Hz, 2 H) 4.4 (q,  $J=7.0$  Hz, 2 H) 5.1 (s, 2 H)  
6.9 (s, 1 H)

### PREPARATION 8

#### **Isopropyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

The final product of Preparation 5 (1.00g, 5.46 mmol), isopropanol (0.42 mL, 5.46 mmol), DEAD (0.86 mL, 5.46 mmol) and triphenylphosphine (1.43g, 5.46 mmol) are suspended in tetrahydrofuran (60 mL) and stirred overnight under inert atmosphere at room temperature. The solvent is evaporated under reduced pressure and the residue purified through a flash chromatography column, eluting with 2:1 hexane/ethyl acetate. The desired final compound is obtained in a quantitative yield.

10  $\delta$  (CDCl<sub>3</sub>) : 1.4 (m, 9 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 5.0 (s, 2 H) 5.2 (m, 1 H) 6.9 (s, 1 H)

### PREPARATION 9

#### **Pyridin-2-ylmethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

15 Obtained (29%) as described in Preparation 7 but using 2-chloromethylpyridine chlorhydrate instead of ethyl bromide.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.2$  Hz, 3 H) 4.3 (q,  $J=7.2$  Hz, 2 H) 5.1 (s, 2 H) 5.5 (s, 2 H) 7.0 (s, 1 H) 7.3 (m, 1 H) 7.4 (d,  $J=8.1$  Hz, 1 H) 7.7 (t,  $J=7.4$  Hz, 1 H) 8.6 (d,  $J=3.0$  Hz, 1 H)

20

### PREPARATION 10

#### **Thiophen-3-ylmethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (90%) as described in Preparation 8 but using 3-hydroxymethylthiophene instead of isopropanol.

25  $\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.2$  Hz, 3 H) 4.3 (q,  $J=7.4$  Hz, 2 H) 5.0 (s, 2 H) 5.4 (s, 2 H) 6.9 (s, 1 H) 7.2 (s, 1 H) 7.3 (s, 1 H) 7.4 (s, 1 H)

### PREPARATION 11

#### **3-Methoxybenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (32%) as described in Preparation 7 but using 3-methoxybenzylchloride instead of ethyl bromide.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.1$  Hz, 3 H) 3.8 (s, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.0 (s, 2 H) 5.4 (s, 2 H) 6.9 (d,  $J=5.8$  Hz, 1 H) 6.9 (s, 1 H) 7.0 (m, 2 H) 7.3 (t,  $J=7.8$  Hz, 1 H)

35

## PREPARATION 12

### **3-Chlorobenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (12%) as described in Preparation 7 but using 3-chlorobenzylbromide  
5 instead of ethyl bromide.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.1$  Hz, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.1 (s, 2 H) 5.3 (s, 2 H) 6.9 (s, 1 H) 7.3 (s, 3 H) 7.4 (s, 1 H)

## PREPARATION 13

10

### **1-Phenylethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (45%) as described in Preparation 7 but using 2-bromoethylbenzene instead of ethyl bromide.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.3$  Hz, 3 H) 1.7 (d,  $J=6.6$  Hz, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.0  
15 (s, 2 H) 6.1 (q,  $J=6.4$  Hz, 1 H) 6.9 (s, 1 H) 7.4 (m, 5 H)

## PREPARATION 14

### **1-Pyridin-4-ylethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

20 Obtained (78%) as described in Preparation 8 but using 1-pyridin-4-ylethanol instead of isopropanol.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.1$  Hz, 3 H) 1.7 (d,  $J=6.6$  Hz, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.1 (s, 2 H) 6.1 (q,  $J=6.6$  Hz, 1 H) 6.9 (s, 1 H) 7.3 (d,  $J=6.0$  Hz, 2 H) 8.6 (d,  $J=5.8$  Hz, 2 H)

25

## PREPARATION 15

### **Indan-1-yl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (50%) as described in Preparation 8 but using indan-1-ol instead of isopropanol.

30  $\delta$  (CDCl<sub>3</sub>) : 1.4 (t,  $J=7.1$  Hz, 3 H) 2.3 (m, 1 H) 2.6 (m, 1 H) 2.9 (m, 1 H) 3.2 (m, 1 H) 4.3 (q, 2 H) 5.0 (s, 2 H) 6.4 (dd,  $J=7.0, 3.7$  Hz, 1 H) 6.9 (s, 1 H) 7.2 (m, 1 H) 7.3 (m, 2 H) 7.5 (d,  $J=7.4$  Hz, 1 H).

## PREPARATION 16

35

**4-Acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid**

A mixture of the title compound of Preparation 4 (3.46 g, 13.66 mmol) and 1 N sodium hydroxide (60 mL) in 120 mL of ethanol was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the crude acidified with 1 N hydrogen chloride (60 mL). The solution was extracted with ethyl acetate and the organic phase dried over sodium sulphate anhydride and concentrated to yield the title compound (2.45 g, 80 % yield) as a white solid.

$\delta$  (CDCl<sub>3</sub>) : 1.4 (t, 3 H), 2.4 (bs, 3 H), 4.2 (q, 2 H).

10

**PREPARATION 17****2-(Dimethylamino)-2-oxoethyl-4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

To a suspension of the title compound of Preparation 16 (400 mg, 1.78 mmol) and anhydrous potassium carbonate (245 mg, 1.78 mmol) in dry dimethylformamide (10 mL) was added 2-chloro-*N,N*-dimethylacetamide (366 mg, 3.55 mmol) and the resulting mixture was stirred at 50 °C for eight hours. The residue was suspended in water and ethyl acetate was added. The organic layer was washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> anhydride and evaporated. The residue obtained was purified by column chromatography (silica gel, hexane/ethyl acetate 1:1) to yield the title compound (310 mg, 56 % yield).

LRMS: *m/z* 311 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.4 (s, 3 H) 3.0 (m, 6 H) 4.2 (q, 2 H) 5.0 (s, 2 H) 7.3 (m, 2 H).

25

**PREPARATION 18****2-Methoxy-1-methyl-2-oxoethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

To a suspension of the title compound of Preparation 16 (300 mg, 1.33 mmol) and anhydrous potassium carbonate (184 mg, 1.33 mmol) in dry dimethylformamide (10 mL) was added methyl 2-bromopropionate (667 mg, 3.99 mmol) and the resulting mixture was stirred at room temperature for four hours. The residue was suspended in water and ethyl acetate was added. The organic layer was washed with water, brine, dried over Na<sub>2</sub>SO<sub>4</sub> anhydride and evaporated to yield the title compound (270 mg, 65 % yield).

35

LRMS: m/Z 312 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.2 (t, 3 H) 1.6 (d, 3 H) 2.4 (s, 3 H) 3.8 (s, 3 H) 4.2 (q, 2 H) 5.3 (m, 1 H) 7.4 (br.s, 2H).

5

#### PREPARATION 19

##### **Benzyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (43%) from the title compound from Preparation 16 and benzylbromide following the experimental procedure described in Preparation 18.

10

LRMS: m/Z 316 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.2 (s, 3 H) 4.2 (q, 2 H) 5.4 (s, 2 H) 7.5 (m, 7 H).

#### PREPARATION 20

##### **Methyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (50%) from the title compound from Preparation 16 and iodomethane following the experimental procedure described in Preparation 18.

LRMS: m/Z 240 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.3 (s, 3 H) 4.0 (s, 3 H) 4.2 (q, 2 H) 7.5 (br.s, 2 H).

20

#### PREPARATION 21

##### **Cyclopropylmethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

25 Obtained (68%) from the title compound from Preparation 16 and (bromomethyl)cyclopropane following the experimental procedure described in Preparation 17.

$\delta$  (CDCl<sub>3</sub>): 0.4 (m, 2 H) 0.6 (m, 2 H), 1.2 (m, 1 H) 1.4 (t, 3 H) 2.4 (s, 3 H) 4.2 (m, 4 H) 7.5 (br.s, 2 H).

30

#### PREPARATION 22

##### **3-Methylbutyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (61.5%) from the title compound from Preparation 16 and 1-bromo-3-methylbutane following the experimental procedure described in Preparation 17.

35

$\delta$  (CDCl<sub>3</sub>): 0.9 (m, 6 H) 1.4 (t, 3 H), 1.7 (m, 3 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 4.4 (m, 2 H) 7.5 (br.s, 2 H).

#### PREPARATION 23

5

##### **2-Methoxyethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (48%) from the title compound from Preparation 16 and 1-bromo-2-methoxyethane following the experimental procedure described in Preparation 17.

$\delta$  (CDCl<sub>3</sub>): 0.9 (m, 6 H) 1.4 (t, 3 H), 1.7 (m, 3 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 4.4 (m, 2 H) 7.5 (br.s, 2 H).

#### PREPARATION 24

##### **2-Phenylethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (65.5%) from the title compound from Preparation 16 and (2-bromoethyl)benzene following the experimental procedure described in Preparation 17.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H), 2.1 (s, 3 H) 3.1 (t, 2 H) 4.2 (q, 2 H) 4.6 (t, 2 H) 7.3 (m, 5 H) 7.5 (br.s, 2 H).

20

#### PREPARATION 25

##### **1-Methyl-2-phenylethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (52%) from the title compound from Preparation 16 and (2-bromopropyl)benzene following the experimental procedure described in Preparation 17.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H), 2.05 (s, 3 H) 2.9 (dd, 1 H) 3.1 (dd, 1H) 4.2 (q, 2 H) 5.4 (m, 1 H) 7.2 (m, 5 H) 7.5 (br.s, 2 H).

#### PREPARATION 26

30

##### **1-Phenylethyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (97.7%) from the title compound from Preparation 16 and (1-bromoethyl)benzene following the experimental procedure described in Preparation 17.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H), 1.7 (d, 3 H) 2.1 (s, 3 H) 4.2 (q, 2 H) 6.1 (q, 1 H) 7.4 (m, 7 H).

### PREPARATION 27

#### **Cyclobutyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

5 To a solution of  $\text{PPh}_3$  (349 mg, 1.33 mmol), cyclobutanol (0.104 mL, 1.33 mmol), and the compound of Preparation 16 (300 mg, 1.33 mmol) in 10 mL dry THF under nitrogen was added DEAD (0.21 mL, 1.33 mmol) and the resulting mixture was stirred at room temperature overnight. Then solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 9:1) to yield the title  
10 compound (248 mg, 67 % yield).

LRMS: m/Z 280 (M+1)+.

Retention Time: 7.4 min.

### PREPARATION 28

15

#### **Cyclohexyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (36%) from the title compound from Preparation 16 and cyclohexanol following the experimental procedure described in Preparation 27.

LRMS: m/Z 308 (M+1)+.

20  $\delta$  (  $\text{CDCl}_3$  ): 1.2-2.0 (m, 13 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 5.0 (m, 1 H) 7.5 (br.s, 2H).

### PREPARATION 29

#### **sec-Butyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

25 Obtained (91%) from the title compound from Preparation 16 and sec-butanol following the experimental procedure described in Preparation 27.

LRMS: m/Z 282 (M+1)+.

$\delta$  (  $\text{CDCl}_3$  ): 1.0 (t, 3 H) 1.4 (m, 6 H) 1.7 (m, 2 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 5.1 (m, 1 H) 7.5 (br.s, 2H).

30

### PREPARATION 30

#### **6-Ethyl-3-methyl-7-oxo-6,7-dihydro-isoxazolo[3,4-d]pyridazine-4-carboxylic acid**

To a stirred solution of the title compound of Preparation 3 (1.5 g, 5.97 mmol) in 45  
35 mL of a 2:1 methanol/THF mixture, a solution of lithium hydroxide (0.57 g, 23.88 mmol) in

8 mL of water was added dropwise. The final mixture was stirred at room temperature for 1 hour and then diluted with some water and acidified with HCl 2N. It was extracted with ethyl acetate, dried and solvent removed to yield (89%) the title product.

$\delta$ (DMSO- $d_3$ ): 1.30 (t, 3H), 2.90 (s, 3H), 4.15 (q, 2H).

5

### PREPARATION 31

**Isopropyl 6-ethyl-3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate.**

10 To a solution of  $PPh_3$  (353 mg, 1.34 mmol), propan-2-ol (0.103 mL, 1.34 mmol), and the compound of Preparation 30 (300 mg, 1.34 mmol) in 7 mL of dry THF under nitrogen was added DEAD (0.211 mL, 1.34 mmol) and the resulting mixture was stirred at room temperature overnight. Then solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate 6:4) to yield the title  
15 compound (220 mg, 62 % yield).

LRMS: m/Z 266 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (m, 9 H) 3.0 (s, 3 H) 4.3 (q, 2 H) 5.3 (q, 1 H).

### PREPARATION 32

20

**Isopropyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

A mixture of the title compound of Preparation 31 (214 mg, 0.8 mmol) and 20% palladium on charcoal (43 mg) in ethanol (10 mL) was shaken under hydrogen at room temperature and 2 bar for 5 h. The catalyst was filtered off and the solvent was removed  
25 under reduced pressure to yield the title compound (214 mg, 99% yield).

LRMS: m/Z 268 (M+1)+.

$\delta$  (DMSO- $D_6$ ): 1.1 (m, 9 H) 2.2 (s, 3 H) 3.9 (q, 2 H) 4.9 (m, 1 H) 7.4 (m, 2H).

### PREPARATION 33

30

**tert-Butyl 6-ethyl-3-methyl-7-oxo-6,7-dihydroisoxazolo[3,4-d]pyridazine-4-carboxylate.**

The title compound of Preparation 30 (300 mg, 1.34 mmol) was dissolved in 30 mL dry toluene and heated to reflux. Then N,N-dimethylformamide di-*t*-butyl acetal (1.29 mL,  
35 5.38 mmol) was added dropwise to the refluxing mixture within 20 min. The solution was

refluxed for a further 40 min, cooled, and washed with water, saturated sodium hydrogen carbonate solution and brine. The organic layer is dried with sodium sulphate anhydride and the solvent evaporated to give an orange solid (204 mg, 54% yield).

LRMS: m/Z 280 (M+1)+.

5  $\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 1.3 (m, 9 H) 3.0 (s, 3 H) 4.3 (q, 2 H).

#### PREPARATION 34

##### **tert-Butyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

10 Obtained (65%) from the title compound of Preparation 33 and following the experimental procedure described in Preparation 32.

LRMS: m/Z 282 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 1.6 (m, 9 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 7.4 (br.s, 2H).

#### 15 PREPARATION 35

##### **Benzyloxycarbonylmethyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

5-Amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (0.6g, 3.3 mmol, see Preparation 5), benzyl bromoacetate (1.6ml, 4.8 mmol), and potassium carbonate (0.5g, 3.3 mmol) were suspended in dimethylformamide (30 ml) and heated overnight at 50°C. The solvent was evaporated under reduced pressure and the residue was passed through a silica-gel column, eluting with hexane/ethyl acetate 3:2, to yield 1.0g of the desired final product. Yield= 92%

25  $\delta$  (CDCl<sub>3</sub>): 1.4 (t, J=7.3 Hz, 3 H) 4.3 (q, J=7.3 Hz, 2 H) 4.9 (s, 2 H) 5.1 (s, 2 H) 5.2 (s, 2 H) 7.0 (m, 1 H) 7.4 (s, 5 H)

#### PREPARATION 36

##### **30 Ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 7 (1.9 g, 9.1 mmol), 4-bromoisquinoline (2.3 g, 10.9 mmol), copper(I)iodide (173 mg, 0.9 mmol), potassium carbonate (2.6g, 19.0 mmol) and 1,1'-dimethylethilenediamine (194  $\mu$ l, 1.8 mmol) in dioxane (10 ml) was heated at 120 °C in a sealed tube under nitrogen for 48h. Once at room temperature, the inorganic salts were filtered and the solvent evaporated under

35

reduced pressure. Purification of the residue through a flash chromatography column eluting with 2:1 hexane/ethyl acetate to 1:2 yielded 823 mg of the desired final compound. Yield= 27%.

5  $\delta$  (CDCl<sub>3</sub>): 1.3 (t,  $J=7.3$  Hz, 3 H) 1.5 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 4.4 (q,  $J=7.3$  Hz, 2 H) 6.9 (s, 1 H) 7.8 (m, 3 H) 7.9 (d, 1 H) 8.1 (d, 1H) 8.6 (bs, 1H) 9.2 (bs, 1H)

#### PREPARATION 37

##### **1-Ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylic acid**

10 The title compound of Preparation 36 (823 mg, 2.4 mmol) was suspended in ethanol (70 ml) and NaOH 2N (3.7 ml, 7.3 mmol) was added. This mixture was stirred overnight at room temperature. The solvent was evaporated under reduced pressure and redissolved in water. This solution was neutralised with HCl 2N. A solid precipitated, which was filtered, washed with water and dried at 50°C under reduced pressure. 637 mg of the  
15 desired final product were obtained. Yield= 84%

$\delta$  (CDCl<sub>3</sub>): 1.3 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 6.3 (s, 1 H) 7.8 (m, 3 H) 8.3 (d, 1H) 8.5 (s, 1H) 9.2 (s, 1H) 9.3 (s, 1H)

#### PREPARATION 38

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##### **4-Bromobenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.5 g, 2.73 mmol), 4-bromobenzyl bromide (819 mg, 3.27 mmol) and potassium carbonate (377 mg, 2.73 mmol) in dimethylformamide (30 ml) was heated at 50 °C for 24h. Once the solvent was  
25 evaporated under reduced pressure, the residue was purified through a flash chromatography column (2:3 hexane/ethyl acetate as eluent) to yield 0.82g of the desired final compound. Yield= 86%

$\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.0 (s, 2 H) 5.3 (s, 2 H) 6.9 (s, 1 H) 7.3 (d,  $J=8.5$  Hz, 2 H) 7.5 (d,  $J=8.5$  Hz, 2 H)

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#### PREPARATION 39

##### **2-Chlorobenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.5 g, 2.73 mmol), 2-chlorobenzyl  
35 bromide (425  $\mu$ l, 3.27 mmol) and potassium carbonate (377 mg, 2.73 mmol) in

dimethylformamide (30 ml) was heated at 50 °C for 24h. Once the solvent was evaporated under reduced pressure, the residue was purified through a flash chromatography column (1:1 hexane/ethyl acetate as eluent) to yield 0.60g of the desired final compound. Yield= 71%

- 5  $\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.0 (s, 2 H) 5.5 (s, 2 H) 6.9 (s, 1 H) 7.4 (m, 4 H)

#### PREPARATION 40

##### 10 **3-Methylbenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.5 g, 2.73 mmol), 2-methylbenzyl chloride (361  $\mu$ l, 2.73 mmol) and potassium carbonate (377 mg, 2.73 mmol) in dimethylformamide (30 ml) was heated at 50 °C for 24h. Once the solvent was evaporated under reduced pressure, the residue was purified through a flash chromatography column (1:1 hexane/ethyl acetate as eluent) to yield 0.12g of the desired final compound. Yield= 16%.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.1$  Hz, 3 H) 2.4 (s, 3 H) 4.3 (q,  $J=7.1$  Hz, 2 H) 5.0 (s, 2 H) 5.3 (s, 2 H) 6.9 (s, 1 H) 7.2 (m, 4 H)

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#### PREPARATION 41

##### **3-Trifluoromethylbenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.5 g, 2.73 mmol), 3-trifluoromethylbenzyl bromide (417  $\mu$ l, 2.73 mmol) and potassium carbonate (377 mg, 2.73 mmol) in dimethylformamide (30 ml) was heated at 50 °C for 24h. Once the solvent was evaporated under reduced pressure, the residue was purified through a flash chromatography column (1:1 hexane/ethyl acetate as eluent) to yield 0.74g of the desired final compound. Yield= 79%.

- 25  $\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 5.1 (s, 2 H) 5.4 (s, 2 H) 6.9 (s, 1 H)  
30 7.5 (d,  $J=7.4$  Hz, 1 H) 7.6 (m, 2 H) 7.7 (s, 1 H)

#### PREPARATION 42

##### **3-Cyanobenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.3 g, 1.64 mmol), 3-cyanobenzyl bromide (385 mg, 1.96 mmol) and potassium carbonate (226 mg, 1.64 mmol) in dimethylformamide (20 ml) was heated at 50 °C for 24h. Once the solvent was evaporated under reduced pressure, the residue was purified through a flash chromatography column (2:1 to 1:1 hexane/ethyl acetate as eluent) to yield 391 mg of the desired final compound. Yield= 80%.

LRMS: m/Z 299 (M+1)<sup>+</sup>

### PREPARATION 43

#### **4-Methoxybenzyl 5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 5 (0.3 g, 1.64 mmol), 4-methoxybenzyl chloride (666 µl, 4.91 mmol) and potassium carbonate (226 mg, 1.64 mmol) in dimethylformamide (20 ml) was heated at 50 °C for 24h. Once the solvent was evaporated under reduced pressure, the residue was purified through a flash chromatography column (1:1 hexane/ethyl acetate as eluent) to yield 180 mg of the desired final compound. Yield= 36%.

δ (CDCl<sub>3</sub>): 1.4 (t, J=7.1 Hz, 3 H) 3.8 (s, 3 H) 4.3 (q, J=7.1 Hz, 2 H) 5.0 (s, 2 H) 5.3 (s, 2 H) 6.9 (m, 3 H) 7.4 (d, J=8.5 Hz, 2 H)

### PREPARATION 44

#### **(S)-2-tert-butoxycarbonylamino-4-methyl-pentanoyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

The title compound of Preparation 37 (200 mg, 0.64 mmol), chloromethyl 2-tert-butoxycarbonylamino-4-methylpentanoate (540 mg, 1.93 mmol) and potassium carbonate (89 mg, 0.64 mmol) were suspended in dimethylformamide (5 ml) and heated overnight at 50°C. The solvent was evaporated under reduced pressure and the residue was passed through a silica-gel column, eluting with hexane/ethyl acetate 1:1, to yield 319 mg of the desired final product. Yield= 87%.

δ (DMSO-d<sub>6</sub>): 0.8 (dd, J=15.3, 6.7 Hz, 6 H) 1.2 (s, 2 H) 1.3 (s, 9 H) 1.4 (t, J=7.0 Hz, 3 H) 1.5 (m, 2 H) 3.9 (m, 1 H) 4.3 (q, J=7.0 Hz, 2 H) 5.8 (d, J=5.9 Hz, 1 H) 5.9 (d, J=6.3 Hz, 1 H) 6.2 (s, 1 H) 7.3 (d, J=7.4 Hz, 1 H) 7.8 (m, 2 H) 8.3 (d, J=7.8 Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

PREPARATION 45**1,3,3-Trimethylbutyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

5        Obtained (50%) from the title compound from Preparation 16 and 4,4-dimethyl-2-pentanol following the experimental procedure described in Preparation 27.

LRMS: m/Z 324 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.0 (s, 9 H) 1.4 (m, 6 H) 1.5 (m, 1 H) 1.8 (m, 1 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 5.3 (m, 1 H) 7.4 (br.s, 2H).

10

PREPARATION 46**3-Chlorobenzyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

15        Obtained (47%) from the title compound from Preparation 16 and 3-chlorobenzyl bromide following the experimental procedure described in Preparation 17.

LRMS: m/Z 350 (M+1)+.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.2 (s, 3 H) 4.2 (q, 2 H) 5.4 (s, 2 H) 7.3 (m, 2 H) 7.5 (br s, 2 H).

PREPARATION 47

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**3-Methoxybenzyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained (37%) from the title compound from Preparation 16 and 3-methoxybenzyl chloride following the experimental procedure described in Preparation 17.

25         $\delta$  (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.2 (s, 3 H) 3.8 (s, 3 H) 4.2 (q, 2 H) 5.4 (s, 2 H) 6.9 (m, 1H) 7.0 (m, 2 H) 7.3 (m, 1H) 7.5 (br.s, 2 H).

PREPARATION 48**30    Octyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (94%) as described in Preparation 18 but using 1-bromooctane instead of ethyl bromide.

$\delta$  (CDCl<sub>3</sub>): 0.9 (m, 3 H) 1.2 (m, 10 H) 1.4 (t, 3 H) 1.8 (m, 2 H) 2.3 (s, 3 H) 4.2 (q, 2 H) 4.4 (t, 2 H) 7.5 (br.s, 2 H)

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PREPARATION 49**(4E)-1,5-Dimethylhept-4-en-1-yl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

5            Obtained (75%) as described in Preparation 27 but using 6-methylhept-5-en-2-ol instead of isopropanol.

δ (CDCl<sub>3</sub>): 0.4 (m, 6 H) 0.6 (m, 4 H) 0.7 (m, 3 H) 0.8 (m, 1 H) 2.1 (m, 2 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 5.2 (m, 2 H) 7.5 (br.s, 2 H)

10

PREPARATION 50**Allyl 4-acetyl-5-amino-1-ethyl-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained (42%) as described in Preparation 18 but using 3-bromoprop-1-ene instead of ethyl bromide.

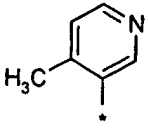

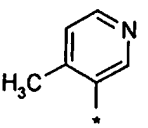
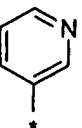
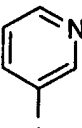
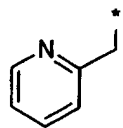
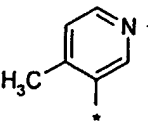
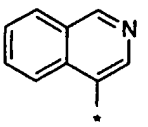
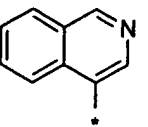
15    δ (CDCl<sub>3</sub>): 1.4 (t, 3 H) 2.4 (s, 3 H) 4.2 (q, 2 H) 4.8 (d, 2 H) 5.38 (d,d, 1 H) 5.42 (d,d, 1 H) 6.0 (m, 1 H) 7.5 (br.s, 2 H)

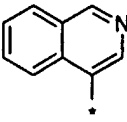
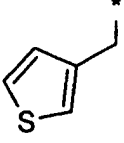
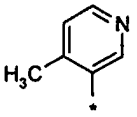
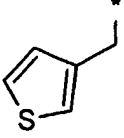
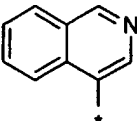
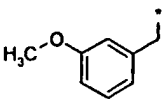
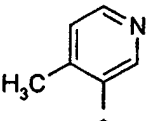
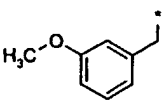
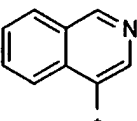
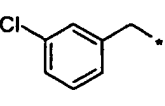
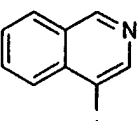
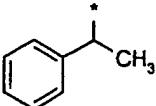
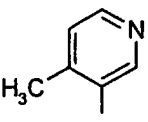
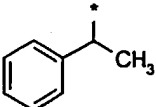
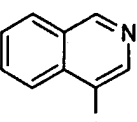
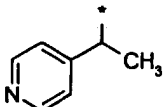
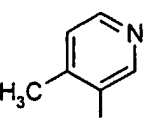
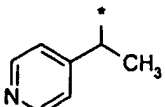
EXAMPLES

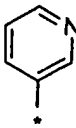
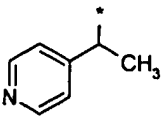
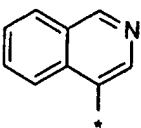
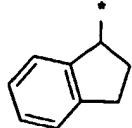
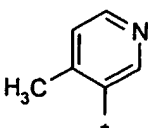
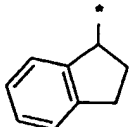
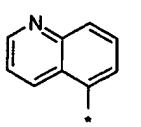
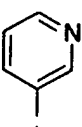
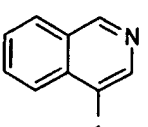
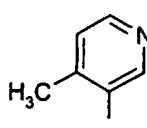
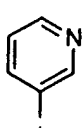
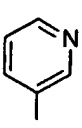
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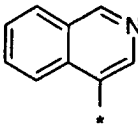
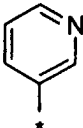
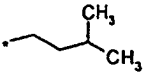
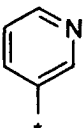
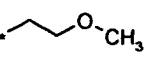
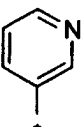
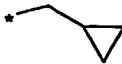
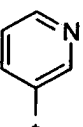
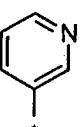
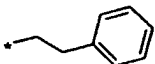
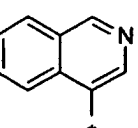
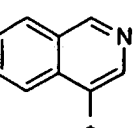
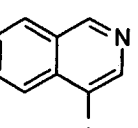
Acronym	Meaning
Et	Ethyl
iPr	Isopropyl
Bn	Benzyl
Ac	Acetyl
Me	Methyl
cHex	Cyclohexyl
t-Bu	<i>tert</i> -Butyl

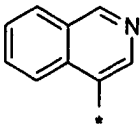

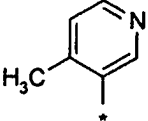
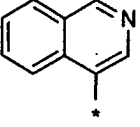
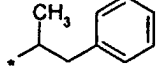
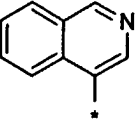
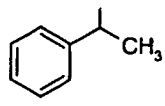
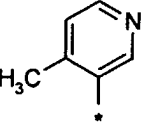
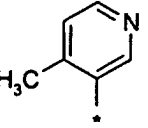
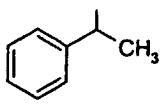
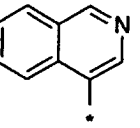
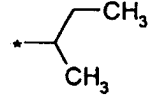
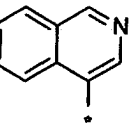
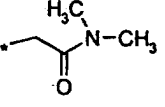
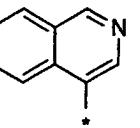
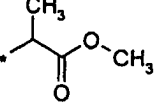
Table 2

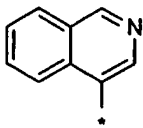
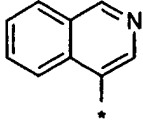
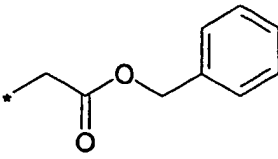
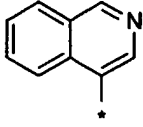
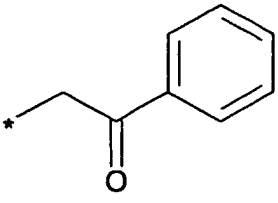
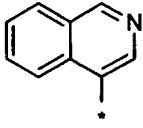
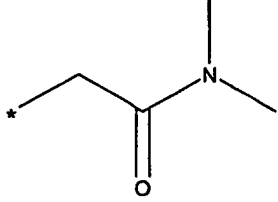
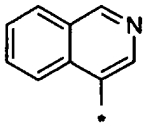
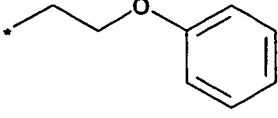
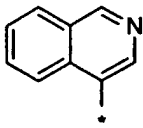
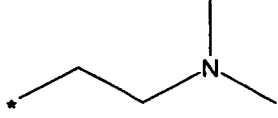
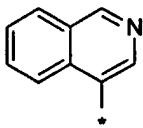
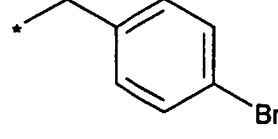
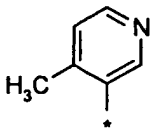
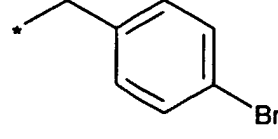
Example	R1	R2	R3	R4
1	Et		H	Bn
2	Et		H	Et
3	Et		H	Et
4	Et		H	iPr
5	Et		H	
6	Et		H	iPr
7	Et		H	Et
8	Et		H	iPr

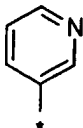
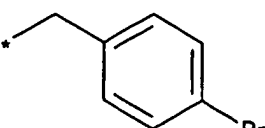
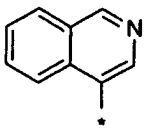
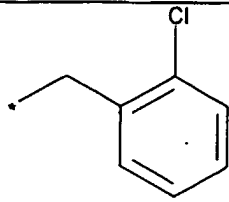
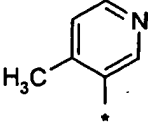
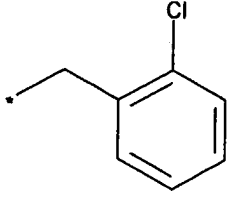
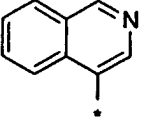
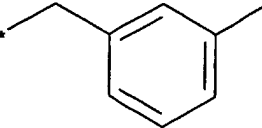
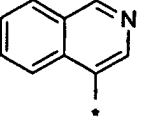
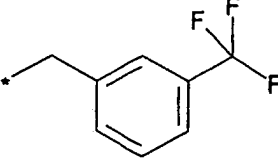
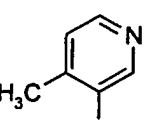
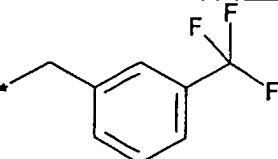
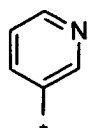
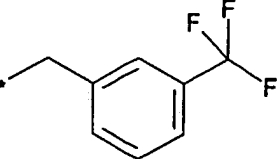
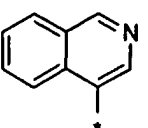
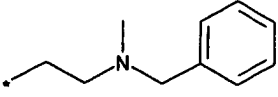
9	Et		H	
10	Et		H	
11	Et		H	
12	Et		H	
13	Et		H	
14	Et		H	
15	Et		H	
16	Et		H	
17	Et		H	

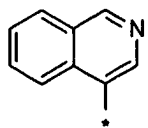
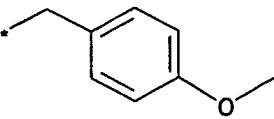
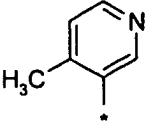
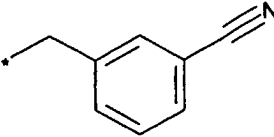
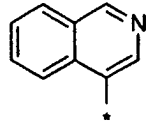
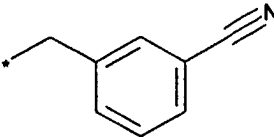
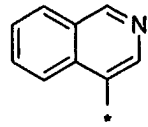
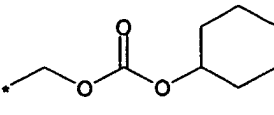
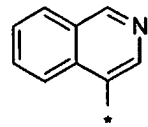
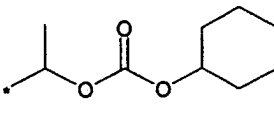
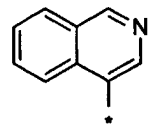
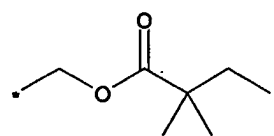
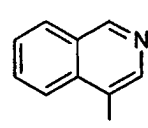
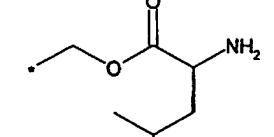
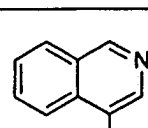
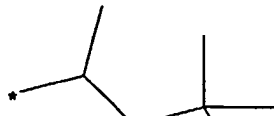
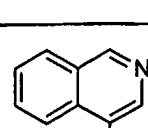
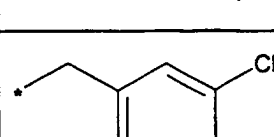
18	Et		H	
19	Et		H	
20	Et		H	
21	Et		Ac	Et
22	Et		Ac	Et
23	Et		Ac	Et
24	Et		Ac	Et
25	Et		Ac	iPr
26	Et		Ac	Bn

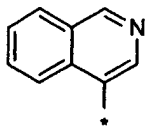
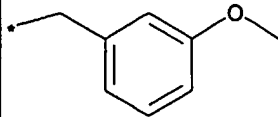
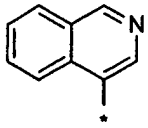
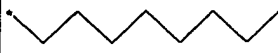
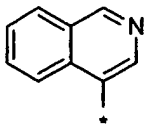
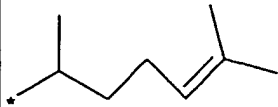
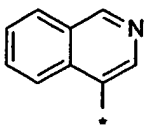
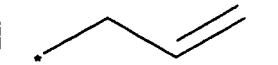
27	Et		Ac	iPr
28	Et		Ac	
29	Et		Ac	
30	Et		Ac	
31	Et		Ac	Me
32	Et		Ac	
33	Et		Ac	Bn
34	Et		Ac	cHex
35	Et		Ac	t-Bu

36	Et		Ac	
37	Et		Ac	cHex
38	Et		Ac	
38	Et		Ac	
40	Et		Ac	t-Bu
41	Et		Ac	
42	Et		Ac	
43	Et		Ac	
44	Et		Ac	

45	Et		H	Bn
46	Et		H	
47	Et		H	
48	Et		H	
49	Et		H	
50	Et		H	
51	Et		H	
52	Et		H	

53	Et		H	
54	Et		H	
55	Et		H	
56	Et		H	
57	Et		H	
58	Et		H	
59	Et		H	
60	Et		H	

61	Et		H	
62	Et		H	
63	Et		H	
64	Et		H	
65	Et		H	
66	Et		H	
67	Et		H	
68	Et		Ac	
69	Et		Ac	

70	Et		Ac	
71	Et		Ac	
72	Et		Ac	
73	Et		Ac	

EXAMPLESEXAMPLE 1

**5 Benzyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 6 (0.30g, 1.10 mmol), 3-bromo-4-methylpyridine (0.15 mL, 1.32 mmol), copper(I)iodide (21 mg, 0.11 mmol), potassium carbonate (0.32g, 2.31 mmol) and 1,1'-dimethylethilenediamine (0.023 mL, 0.22 mmol) in dioxane (2 mL) are heated at 120 °C in a sealed tube under nitrogen for 48h. Once at room temperature, the inorganic salts are filtered and the solvent evaporated under reduced pressure. Purification of the residue through a flash chromatography column eluting with 2:1 hexane/ethyl acetate to 1:1 yields 80 mg of the desired final compound. Yield= 20%.

15  $\delta$  (CDCl<sub>3</sub>): 1.5 (t, J=7.3 Hz, 3 H) 2.3 (s, 3 H) 4.4 (q, J=7.3 Hz, 2 H) 5.4 (s, 2 H) 6.8 (s, 1 H) 7.2 (d, J=5.0 Hz, 1 H) 7.4 (m, 6 H) 8.4 (d, J=4.6 Hz, 1 H) 8.6 (s, 1 H)  
m.p. 137.4-138.1°C

EXAMPLE 2

**Ethyl 1-ethyl-5-(pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 7 (0.21g, 0.99 mmol), 3-bromopyridine (0.12 mL, 1.19 mmol), copper(I)iodide (19 mg, 0.10 mmol), potassium carbonate (0.29g, 2.09 mmol) and 1,1'-dimethylethilenediamine (0.021 mL, 0.20 mmol) in dioxane (2 mL) are heated at 120 °C in a sealed tube under nitrogen for 48h. Once at room temperature, the inorganic salts are filtered and the solvent evaporated under reduced pressure. Purification of the residue through a flash chromatography column eluting with 2:1 hexane/ethyl acetate to 1:1 yields 97 mg of the desired final compound. Yield= 34%.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 1.5 (t,  $J=7.3$  Hz, 3 H) 4.4 (q,  $J=7.3$  Hz, 2 H) 4.4 (q,  $J=7.0$  Hz, 2 H) 7.3 (s, 1 H) 7.4 (dd,  $J=7.9, 4.6$  Hz, 1 H) 7.6 (m, 2 H) 8.5 (d,  $J=6.2$  Hz, 1 H) 8.6 (d,  $J=2.5$  Hz, 1 H)

m.p. 166.1-166.9°C

**EXAMPLE 3****Ethyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (37%) from the title compound of Preparation 7 and the corresponding bromide following the procedure of Example 1.

$\delta$  (CDCl<sub>3</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 1.5 (t,  $J=7.3$  Hz, 3 H) 2.3 (s, 3 H) 4.4 (m, 4 H) 6.9 (s, 1 H) 7.3 (m, 2 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.6 (s, 1 H)

m.p. 186.6-187.3°C

**EXAMPLE 4****Isopropyl 1-ethyl-5-(pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (23%) from the title compound of Preparation 8 and the corresponding bromide following the procedure of Example 2.

$\delta$  (CDCl<sub>3</sub>): 1.4 (d,  $J=6.2$  Hz, 6 H) 1.5 (t,  $J=7.3$  Hz, 3 H) 4.4 (q,  $J=7.5$  Hz, 2 H) 5.2 (m, 1 H) 7.3 (s, 1 H) 7.4 (dd,  $J=8.3, 4.6$  Hz, 1 H) 7.6 (m, 2 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.6 (d,  $J=2.5$  Hz, 1 H)

m.p. 131.8-133.1°C

**EXAMPLE 5**

**Isopropyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (21%) from the title compound of Preparation 8 and the corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO-d<sub>6</sub>): 1.2 (d,  $J=6.2$  Hz, 6 H) 1.3 (t,  $J=7.0$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.0 (m, 1 H) 6.3 (s, 1 H) 7.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (s, 1 H) 8.8 (s, 1 H)

m.p. 179.9-181.3°C

**EXAMPLE 6**

**Pyridin-2-ylmethyl 1-ethyl-5-(pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (16%) from the title compound of Preparation 9 and the corresponding bromide following the procedure of Example 2.

$\delta$  (CDCl<sub>3</sub>): 1.5 (t,  $J=7.3$  Hz, 3 H) 4.4 (t,  $J=7.5$  Hz, 2 H) 5.5 (s, 2 H) 7.2 (m, 1 H) 7.4 (m, 2 H) 7.4 (d,  $J=7.9$  Hz, 1 H) 7.6 (m, 2 H) 7.7 (m, 1 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.6 (m, 2 H)

m.p. 146.3-147.5°C

**EXAMPLE 7**

**Isopropyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 8 (0.40g, 1.78 mmol), 4-bromoisoquinoline (0.44 g, 2.13 mmol), copper(I)iodide (34 mg, 0.18 mmol), potassium carbonate (0.52g, 3.73 mmol) and 1,1'-dimethylethilenediamine (0.038 mL, 0.36 mmol) in dioxane (2 mL) are heated at 120 °C in a sealed tube under nitrogen for 48h. Once at room temperature, the inorganic salts are filtered and the solvent evaporated under reduced pressure. Purification of the residue through a flash chromatography column eluting with 2:1 hexane/ethyl acetate to 1:1 yields 99 mg of the desired final compound. Yield= 28%.

$\delta$  (DMSO-d<sub>6</sub>): 1.2 (d,  $J=6.2$  Hz, 6 H) 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 5.0 (m, 1 H) 6.3 (s, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=8.3$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H)

m.p. 191.6-193.0°C

#### EXAMPLE 8

##### 5 **Ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (48%) from the title compound of Preparation 7 and the corresponding bromide following the procedure of Example 7.

$\delta$  (CDCl<sub>3</sub>): 1.3 (t,  $J=7.0$  Hz, 3 H) 1.5 (t,  $J=7.3$  Hz, 3 H) 4.4 (q,  $J=7.0$  Hz, 2 H) 4.4 (q,  $J=7.0$  Hz, 2 H) 6.9 (s, 1 H) 7.7 (m, 2 H) 7.8 (m, 1 H) 7.9 (d,  $J=8.3$  Hz, 1 H) 8.1 (d,  $J=7.9$  Hz, 1 H) 8.7 (s, 1 H) 9.2 (s, 1 H)  
10 m.p. 193.7-194.2°C

#### EXAMPLE 9

##### 15 **Thiophen-3-ylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (16%) from the title compound of Preparation 10 and the corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 4.2 (q,  $J=7.3$  Hz, 2 H) 5.2 (s, 2 H) 6.3 (s, 1 H) 7.0 (d,  $J=5.0$  Hz, 1 H) 7.5 (m, 1 H) 7.5 (dd,  $J=5.0, 2.9$  Hz, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H) 9.3 (s, 1 H)  
20 m.p. 154.3-154.9°C

#### EXAMPLE 10

25

##### **Thiophen-3-ylmethyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (9%) from the title compound of Preparation 10 and the corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.0$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 6.3 (s, 1 H) 7.1 (d,  $J=5.0$  Hz, 1 H) 7.4 (d,  $J=5.0$  Hz, 1 H) 7.5 (m, 2 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (s, 1 H) 8.9 (s, 1 H)  
30 m.p. 141.7-142.9°C

35

#### EXAMPLE 11

**3-Methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (26%) from the title compound of Preparation 11 and the  
5 corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 3.7 (s, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 5.2 (s, 2 H)  
6.3 (s, 1 H) 6.9 (m, 3 H) 7.2 (dd,  $J=8.9, 7.7$  Hz, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5  
(s, 1 H) 9.3 (m, 2 H)

m.p. 153.2-154.3°C

10

EXAMPLE 12

**3-Methoxybenzyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (25%) from the title compound of Preparation 11 and the  
15 corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.3$  Hz, 3 H) 2.2 (s, 3 H) 3.7 (s, 3 H) 4.2 (q,  $J=7.3$  Hz, 2 H)  
5.2 (s, 2 H) 6.3 (s, 1 H) 6.9 (m, 3 H) 7.3 (t,  $J=8.1$  Hz, 1 H) 7.4 (d,  $J=4.6$  Hz, 1 H) 8.4 (d,  
 $J=5.0$  Hz, 1 H) 8.4 (s, 1 H) 8.9 (s, 1 H)

20 m.p. 118.5-119.4°C

EXAMPLE 13

**3-Chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (18%) from the title compound of Preparation 12 and the  
corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 5.2 (s, 2 H) 6.3 (s, 1 H)  
30 7.2 (m, 1 H) 7.4 (m, 3 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 2 H)

m.p. 147.6-148.4°C

EXAMPLE 14

**1-Phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (37%) from the title compound of Preparation 13 and the corresponding bromide following the procedure of Example 7.

5         $\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 1.5 (d,  $J=6.6$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H)  
5.9 (q,  $J=6.6$  Hz, 1 H) 6.3 (s, 1 H) 7.3 (m, 5 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1  
H) 9.3 (s, 1 H) 9.3 (s, 1 H)  
m.p. 166.7-167.6°C

10

EXAMPLE 15

**1-Phenylethyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (37%) from the title compound of Preparation 13 and the  
15 corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.0$  Hz, 3 H) 1.5 (d,  $J=6.6$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.2$   
Hz, 2 H) 6.0 (q,  $J=6.4$  Hz, 1 H) 6.3 (s, 1 H) 7.3 (m, 6 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (s, 1 H)  
8.9 (s, 1 H)  
m.p. 170.3-171.3°C

20

EXAMPLE 16

**1-Pyridin-4-ylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (32%) from the title compound of Preparation 14 and the  
25 corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.3$  Hz, 3 H) 1.5 (d,  $J=6.6$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H)  
5.9 (q,  $J=6.6$  Hz, 1 H) 6.3 (s, 1 H) 7.2 (m, 2 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (m, 3  
30 H) 9.3 (m, 2 H)  
m.p. 186.9-187.7°C

EXAMPLE 17

**1-Pyridin-4-ylethyl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (26%) from the title compound of Preparation 14 and the corresponding bromide following the procedure of Example 1.

5         $\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 1.5 (d,  $J=6.6$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.9 (q,  $J=6.6$  Hz, 1 H) 6.3 (s, 1 H) 7.4 (m, 2 H) 7.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (s, 1 H) 8.6 (m, 2 H) 8.9 (s, 1 H).

m.p. 167.6-168.8°C

10

**EXAMPLE 18**

**1-Pyridin-4-ylethyl 1-ethyl-5-(pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

15        Obtained as a solid (27%) from the title compound of Preparation 14 and the corresponding bromide following the procedure of Example 2.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t,  $J=7.0$  Hz, 3 H) 1.6 (d,  $J=6.7$  Hz, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 6.0 (q,  $J=6.7$  Hz, 1 H) 7.1 (s, 1 H) 7.4 (m, 2 H) 7.5 (dd,  $J=8.4, 4.5$  Hz, 1 H) 7.8 (m, 1 H) 8.4 (dd,  $J=4.7, 1.2$  Hz, 1 H) 8.6 (m, 2 H) 8.6 (d,  $J=2.7$  Hz, 1 H) 9.2 (s, 1 H)

m.p. 98.8-99.9°C

20

**EXAMPLE 19**

**Indan-1-yl 1-ethyl-5-(4-methylpyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

25        Obtained as a solid (7%) from the title compound of Preparation 15 and the corresponding bromide following the procedure of Example 1.

30         $\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.0$  Hz, 3 H) 2.0 (m, 1 H) 2.9 (m, 2 H) 4.2 (q,  $J=7.1$  Hz, 2 H) 6.2 (m, 1 H) 6.3 (s, 1 H) 7.2 (m, 4 H) 7.8 (m, 3 H) 8.2 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

m.p. 174.9-176.2°C

**EXAMPLE 20**

35

**Indan-1-yl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (18%) from the title compound of Preparation 15 and the corresponding bromide following the procedure of Example 7.

5            $\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.3$  Hz, 3 H) 2.0 (m, 1 H) 2.2 (s, 3 H) 2.9 (m, 1 H) 3.0 (m, 1 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 6.3 (dd,  $J=7.0$ , 4.1 Hz, 1 H) 6.3 (s, 1 H) 7.2 (m, 1 H) 7.3 (m, 4 H) 8.4 (d,  $J=5.0$  Hz, 1 H) 8.4 (s, 1 H) 8.8 (s, 1 H)  
m.p. 180.2-182.1°C

10

**EXAMPLE 21**

**Ethyl 4-acetyl-1-ethyl-6-oxo-5-(quinolin-5-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

A mixture of the title compound of Preparation 4 (500 mg, 1.97 mmol), 5-quinolinboronic acid (560 mg, 4.0 mmol), anhydrous cupric acetate (683 mg, 3.95 mmol), triethylamine (0.40 g, 3.95 mmol) and activated molecular sieves (1.46 g, 4 Å) in dry dichloromethane (25 mL) was stirred under air exposure at room temperature for 48 h. The reaction was filtered and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography (53% yield).

20

LRMS:  $m/z$  381 ( $M+1$ )<sup>+</sup>.

$\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.3$  Hz, 3 H) 1.5 (s, 3 H) 4.2 (m, 4 H) 7.3 (d,  $J=7.3$  Hz, 1 H) 7.6 (dd,  $J=8.4$ , 4.1 Hz, 1 H) 7.6 (dd, 1 H) 7.9 (d,  $J=8.6$  Hz, 1 H) 8.4 (d, 1 H) 8.9 (d, 1 H) 9.3 (s, 1 H).

25

**EXAMPLE 22**

**Ethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (12.5%) from the title compound of Preparation 4 and the corresponding 3-bromopyridine following the procedure of Example 2.

30

LRMS:  $m/z$  331 ( $M+1$ )<sup>+</sup>.

$\delta$  (DMSO- $d_6$ ): 1.2 (t,  $J=7.2$  Hz, 3 H) 1.3 (t,  $J=7.2$  Hz, 3 H) 1.9 (s, 3 H) 4.2 (m, 4 H) 7.3 (m, 1 H) 7.4 (m, 1 H) 8.3 (m, 1 H) 8.3 (d,  $J=2.3$  Hz, 1 H) 9.1 (s, 1 H).

EXAMPLE 23**Ethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

5            Obtained as a solid (11%) from the title compound of Preparation 4 and the corresponding 4-bromoisoquinoline following the procedure of Example 7.

LRMS: m/Z 381 (M+1)<sup>+</sup>.

δ (DMSO-d<sub>6</sub>): 1.2 (t, J=7.2 Hz, 3 H) 1.4 (t, J=7.2 Hz, 3 H) 1.6 (s, 3 H) 4.2 (m, 4 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, 1 H) 8.2 (d, 1 H) 8.3 (s, 1 H) 9.2 (m, 1 H).

10

EXAMPLE 24**Ethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

15            Obtained as a solid (6%) from the title compound of Preparation 4 and the corresponding 3-bromo-4-methyl-pyridine following the procedure of Example 1. The product was purified by preparative HPLC/MS.

LRMS: m/Z 345 (M+1)<sup>+</sup>.

20            δ (DMSO-d<sub>6</sub>): 1.2 (t, J=7.2 Hz, 3 H) 1.3 (t, J=7.0 Hz, 3 H) 1.7 (s, 3 H) 2.2 (s, 3 H) 4.2 (m, 5 H) 7.3 (d, J=4.7 Hz, 1 H) 8.2 (s, 1 H) 8.3 (d, J=4.7 Hz, 1 H).

EXAMPLE 25

25            **Isopropyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (14.5%) from the title compound of Preparation 32 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 345 (M+1)<sup>+</sup>.

30            δ (DMSO-d<sub>6</sub>): 1.2 (m, 6 H) 1.25 (t, 3 H) 1.9 (s, 3 H) 4.2 (q, 2 H) 5.0 (m, 1 H) 7.3 (m, 1 H) 7.4 (m, 1 H) 8.3 (br.s, 2 H) 9.2 (s, 1 H).

EXAMPLE 26

35            **Benzyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (20%) from de title compound of Preparation 19 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 393 (M+1)<sup>+</sup>.

5  $\delta$  (DMSO-d<sub>6</sub>): 1.3 (t, J=7.0 Hz, 3 H) 1.9 (s, 3 H) 4.1 (q, J=7.0 Hz, 2 H) 5.2 (m, 2 H) 7.3 (m, 7 H) 8.3 (d, J=3.1 Hz, 1 H) 8.3 (d, J=2.3 Hz, 1 H) 9.1 (m, 1 H).

#### EXAMPLE 27

10 **Isopropyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (5%) from de title compound of Preparation 32 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 395 (M+1)<sup>+</sup>.

Retention Time: 13 min.

15

#### EXAMPLE 28

**3-Methylbutyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

20 Obtained as a solid (23.5%) from de title compound of Preparation 22 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 373 (M+1)<sup>+</sup>.

25  $\delta$  (DMSO-d<sub>6</sub>): 0.9 (s, 3 H) 0.9 (s, 3 H) 1.3 (t, J=7.3 Hz, 3 H) 1.5 (q, J=7.0 Hz, 2 H) 1.7 (m, 1 H) 1.9 (s, 3 H) 4.15 (q, 2H) 4.2 (t, 2H) 7.3 (m, 1 H) 7.4 (d, J=8.3 Hz, 1 H) 8.3 (br.s, 1 H) 9.1 (s, 1 H)

#### EXAMPLE 29

30 **2-Methoxyethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (20%) from de title compound of Preparation 23 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 361 (M+1)<sup>+</sup>.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.3$  Hz, 3 H) 1.9 (s, 3 H) 3.3 (s, 3 H) 3.5 (m, 2 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 4.3 (m, 2 H) 7.3 (m, 1 H) 7.4 (m, 1 H) 8.3 (d,  $J=4.1$  Hz, 1 H) 8.3 (d,  $J=2.1$  Hz, 1 H) 9.1 (s, 1 H).

5

#### EXAMPLE 30

##### **Cyclopropylmethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (24%) from the title compound of Preparation 21 and the corresponding boronic acid following the procedure of Example 21.

LRMS:  $m/z$  357 ( $M+1$ )<sup>+</sup>.

$\delta$  (DMSO-d<sub>6</sub>): 0.3 (m, 2 H) 0.5 (m, 2 H) 1.1 (m, 1 H) 1.3 (t,  $J=7.1$  Hz, 3 H) 1.9 (s, 3 H) 4.0 (d,  $J=7.5$  Hz, 2 H) 4.2 (q,  $J=7.1$  Hz, 2 H) 7.3 (m, 1 H) 7.4 (m, 1 H) 8.3 (m, 2 H) 9.1 (s, 1 H).

15

#### EXAMPLE 31

##### **Methyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (16%) from the title compound of Preparation 20 and the corresponding boronic acid following the procedure of Example 21.

LRMS:  $m/z$  317 ( $M+1$ )<sup>+</sup>.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.2$  Hz, 3 H) 1.9 (s, 3 H) 3.7 (s, 3 H) 4.1 (q,  $J=7.2$  Hz, 2 H) 7.3 (dd,  $J=8.2, 4.7$  Hz, 1 H) 7.4 (dd,  $J=8.2, 1.6$  Hz, 1 H) 8.3 (m, 2 H) 9.1 (br.s, 1 H).

25

#### EXAMPLE 32

##### **2-Phenylethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (22%) from the title compound of Preparation 24 and the corresponding boronic acid following the procedure of Example 21.

LRMS:  $m/z$  407 ( $M+1$ )<sup>+</sup>.

$\delta$  (DMSO-d<sub>6</sub>): 1.3 (t,  $J=7.2$  Hz, 3 H) 1.9 (s, 3 H) 2.9 (t,  $J=6.8$  Hz, 2 H) 4.2 (q,  $J=7.2$  Hz, 2 H) 4.4 (t,  $J=6.8$  Hz, 2 H) 7.3 (m, 6 H) 7.4 (m, 1 H) 8.3 (m,  $J=9.5$  Hz, 2 H) 9.1 (s, 1 H).

35

EXAMPLE 33**5 Benzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (33%) from the title compound of Preparation 19 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 443 (M+1)+.

10  $\delta$  (DMSO-d<sub>6</sub>): 1.4 (t, J=7.0 Hz, 3 H) 1.5 (s, 3 H) 4.2 (q, J=7.0 Hz, 2 H) 5.2 (m, 2 H) 7.3 (m, 5 H) 7.8 (m, 2 H) 8.0 (d, J=8.2 Hz, 1 H) 8.2 (d, J=7.8 Hz, 1 H) 8.3 (m, 1 H) 9.2 (m, 2 H).

EXAMPLE 34**15 Cyclohexyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (11%) from the title compound of Preparation 28 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 435 (M+1)+.

20  $\delta$  (DMSO-d<sub>6</sub>): 1.4 (m, 13 H) 1.6 (s, 3 H) 4.2 (q, J=7.2 Hz, 2 H) 4.7 (m, 1 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, J=8.3 Hz, 1 H) 8.2 (d, J=8.3 Hz, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

EXAMPLE 35

25

***tert*-Butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (16%) from the title compound of Preparation 34 and the corresponding boronic acid following the procedure of Example 21.

30

LRMS: m/Z 409 (M+1)+.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t, J=7.3 Hz, 3 H) 1.4 (s, 9 H) 1.6 (s, 3 H) 4.2 (q, J=7.3 Hz, 2 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, J=8.3 Hz, 1 H) 8.2 (d, J=7.9 Hz, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

EXAMPLE 36

**Cyclobutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

5            Obtained as a solid (5%) from the title compound of Preparation 27 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 407 (M+1)+.

Retention Time: 14 min.

10

EXAMPLE 37

**Cyclohexyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

15            Obtained as a solid (18%) from the title compound of Preparation 28 and 3-bromo-4-methylpyridine following the procedure of Example 1.

LRMS: m/Z 399 (M+1)+.

$\delta$  (DMSO-d<sub>6</sub>): 1.2 (s, 2 H) 1.3 (m, 5 H) 1.4 (m, 2 H) 1.7 (m, 2 H) 1.7 (s, 3 H) 1.8 (m, 2 H) 2.2 (s, 3 H) 4.2 (q, J=7.3 Hz, 2 H) 4.8 (q, 1 H) 7.3 (d, J=5.0 Hz, 1 H) 8.2 (s, 1 H) 8.3 (d, J=5.0 Hz, 1 H) 8.8 (s, 1 H).

20

EXAMPLE 38

**1-Methyl-2-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

25            Obtained as a solid (23%) from the title compound of Preparation 25 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/Z 471 (M+1)+.

30             $\delta$  (DMSO-d<sub>6</sub>): 1.2 (d, J=6.2 Hz, 3 H) 1.4 (t, J=7.0 Hz, 3 H) 1.5 (s, 3 H) 2.9 (m, 2 H) 4.2 (m, 2 H) 5.1 (m, 1 H) 7.2 (m, 5 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 7.9 (d, J=7.5 Hz, 1 H) 8.2 (d, J=7.9 Hz, 1 H) 8.3 (s, 1 H) 9.2 (s, 2 H).

EXAMPLE 39

35            **1-Phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (17%) from the title compound of Preparation 26 and the corresponding boronic acid following the procedure of Example 21.

LRMS: m/z 457 (M+1)+.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t, J=7.3 Hz, 3 H) 1.5 (m, 6 H) 4.2 (m, 2 H) 5.9 (q, J=6.5 Hz, 1 H) 7.3 (m, 5 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, J=7.5 Hz, 1 H) 8.2 (d, J=7.9 Hz, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

#### EXAMPLE 40

##### 10 ***tert*-Butyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (21%) from the title compound of Preparation 34 and 3-bromo-4-methylpyridine following the procedure of Example 1.

LRMS: m/z 373 (M+1)+.

15  $\delta$  (DMSO-d<sub>6</sub>): 1.3 (t, J=7.1 Hz, 3 H) 1.4 (s, 9 H) 1.7 (s, 3 H) 2.2 (s, 3 H) 4.2 (q, J=7.1 Hz, 2 H) 7.2 (d, J=5.0 Hz, 1 H) 8.2 (s, 1 H) 8.3 (d, J=5.0 Hz, 1 H) 8.8 (s, 1 H).

#### EXAMPLE 41

##### 20 **1-Phenylethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (9.6%) from the title compound of Preparation 26 and 3-bromo-4-methylpyridine following the procedure of Example 1.

LRMS: m/z 421 (M+1)+.

25  $\delta$  (DMSO-d<sub>6</sub>): 1.3 (t, J=6.8 Hz, 3 H) 1.5 (d, J=6.7 Hz, 3 H) 1.7 (s, 3 H) 2.2 (s, 3 H) 4.2 (m, 2 H) 5.9 (q, J=6.8 Hz, 1 H) 7.2 (d, J=4.7 Hz, 1 H) 7.3 (m, 5 H) 8.2 (m, 1 H) 8.3 (m, J=3.9 Hz, 1 H) 8.8 (s, 1 H).

#### EXAMPLE 42

30

##### ***sec*-Butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (2%) from the title compound of Preparation 29 and the corresponding boronic acid following the procedure of Example 21. The product was

35 purified by preparative HPLC/MS.

LRMS: m/Z 409 (M+1)+.

Retention Time: 15 min.

#### EXAMPLE 43

5

**2-(Dimethylamino)-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (1.5%) from the title compound of Preparation 17 and the corresponding boronic acid following the procedure of Example 21. The product was

10 purified by preparative HPLC/MS.

LRMS: m/Z 438 (M+1)+.

Retention Time: 10 min.

#### EXAMPLE 44

15

**2-Methoxy-1-methyl-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (19%) from the title compound of Preparation 18 and the corresponding boronic acid following the procedure of Example 21.

20 LRMS: m/Z 439 (M+1)+.

$\delta$  (DMSO-d<sub>6</sub>): 1.4 (t, J=6.9 Hz, 3 H) 1.4 (d, J=7.0 Hz, 3 H) 1.6 (s, 3 H) 3.6 (s, 3 H) 4.2 (q, J=6.9 Hz, 2 H) 5.1 (q, J=7.0 Hz, 1 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 7.9 (d, J=8.6 Hz, 1 H) 8.2 (d, J=8.2 Hz, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

25

#### EXAMPLE 45

**Benzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

A mixture of the title compound of Preparation 35 (330 mg, 1.0 mmol), 4-bromoisquinoline (249 mg, 1.2 mmol), copper(I)iodide (19 mg, 0.10 mmol), potassium carbonate (0.29g, 2.1 mmol) and 1,1'-dimethylethylenediamine (21  $\mu$ l, 0.20 mmol) in dioxane (2 ml) are heated at 125 °C in a sealed tube under nitrogen for 48h. Once at room temperature, the inorganic salts are filtered and the solvent evaporated under reduced pressure. Purification of the residue through a flash chromatography column eluting with 4:1 hexane/ethyl acetate to 1:1 yields 95 mg of the desired final compound. Yield= 24%.

$\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.2$  Hz, 3 H) 4.2 (q,  $J=7.2$  Hz, 2 H) 5.2 (s, 2 H) 6.3 (s, 1 H) 7.3 (m, 5 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m,  $J=3.3$  Hz, 2 H)

#### EXAMPLE 46

5

#### **Benzyloxycarbonylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

The title compound of Preparation 37 (80 mg, 0.26 mmol), benzyl bromoacetate (123  $\mu$ l, 0.77 mmol) and potassium carbonate (36 mg, 0.26 mmol) are suspended in dimethylformamide (4 ml) and heated overnight at 50°C. The solvent is evaporated under reduced pressure and the residue is passed through a silica-gel column, eluting with hexane/ethyl acetate 1:1 to 2:3, to yield 34 mg of the desired final product. Yield= 29%.  
 $\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.0$  Hz, 3 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 4.9 (s, 2 H) 5.1 (s, 2 H) 6.2 (s, 1 H) 7.3 (m, 5 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

15

#### EXAMPLE 47

#### **2-Oxo-2-phenyl-ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (71%) from the title compound of Preparation 37 and the corresponding bromide following the procedure of Example 46.  
 $\delta$  (DMSO- $d_6$ ): 1.4 (m, 3 H) 4.3 (q,  $J=7.2$  Hz, 2 H) 5.6 (s, 2 H) 6.3 (s, 1 H) 7.5 (t,  $J=7.8$  Hz, 2 H) 7.7 (m, 1 H) 7.7 (m, 1 H) 7.8 (m, 2 H) 7.9 (dd,  $J=8.2, 1.2$  Hz, 2 H) 8.2 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H) 9.3 (s, 1 H)

25

#### EXAMPLE 48

#### **Dimethylcarbamoylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (30%) from the title compound of Preparation 37 and the corresponding chloride following the procedure of Example 46.  
 $\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.0$  Hz, 3 H) 2.8 (s, 3 H) 2.9 (s, 3 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 4.9 (s, 2 H) 6.2 (s, 1 H) 7.8 (m, 1 H) 7.8 (m,  $J=4.1$  Hz, 2 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H) 9.3 (s, 1 H)

35

EXAMPLE 49**2-Phenoxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

5            Obtained as a solid (49%) from the title compound of Preparation 37 and the corresponding bromide following the procedure of Example 46.

$\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.2 (m, 2 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 4.5 (m, 2 H) 6.3 (s, 1 H) 6.8 (m,  $J=7.9$  Hz, 2 H) 6.9 (t,  $J=7.5$  Hz, 1 H) 7.3 (m, 2 H) 7.8 (m, 3 H) 8.2 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H) 9.3 (s, 1 H)

10

EXAMPLE 50**2-Dimethylaminoethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

15            The final product of Preparation 37 (80 mg, 0.26 mmol), dimethylaminoethanol (26  $\mu$ l, 0.26 mmol), DEAD (40  $\mu$ l, 0.26 mmol) and triphenylphosphine (68 mg, 0.26 mmol) are suspended in tetrahydrofuran (4 ml) and stirred overnight under inert atmosphere at room temperature. One more equivalent of dimethylaminoethanol, triphenylphosphine and DEAD are added and the reaction mixture is stirred for another 24h. The solvent is  
20 evaporated under reduced pressure and the residue purified through a flash chromatography column, eluting with ethyl acetate first and then with AcOEt/MeOH 7:3. 74 mg of the desired final compound are obtained. Yield= 76%.

$\delta$  (DMSO- $d_6$ ): 1.4 (m, 3 H) 2.0 (s, 6 H) 2.4 (t,  $J=5.5$  Hz, 2 H) 4.2 (t,  $J=5.7$  Hz, 2 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 6.2 (s, 1 H) 7.8 (m, 1 H) 7.8 (m, 2 H) 8.3 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s, 1 H) 9.3 (s, 1 H)

25

EXAMPLE 51**4-Bromobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

30

Obtained as a solid (10%) from the title compound of Preparation 38 and the corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.2 (q,  $J=7.5$  Hz, 2 H) 5.2 (s, 2 H) 6.3 (s, 1 H) 7.3 (d,  $J=8.3$  Hz, 2 H) 7.5 (d,  $J=8.3$  Hz, 2 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (s,

35 2 H)

EXAMPLE 52**4-Bromobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

5            Obtained as a solid (5%) from the title compound of Preparation 38 and the corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.3$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.2$  Hz, 2 H) 6.3 (s, 2 H) 7.4 (m, 3 H) 7.6 (d,  $J=8.7$  Hz, 2 H) 8.4 (m, 3 H) 8.9 (s, 1 H)

10

EXAMPLE 53**4-Bromobenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate**

15            Obtained as a solid (7%) from the title compound of Preparation 38 and the corresponding bromide following the procedure of Example 2.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.2$  Hz, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 7.1 (s, 1 H) 7.4 (m, 3 H) 7.6 (d,  $J=8.2$  Hz, 2 H) 7.8 (d,  $J=8.2$  Hz, 1 H) 8.4 (d,  $J=3.5$  Hz, 1 H) 8.6 (d,  $J=2.3$  Hz, 1 H) 9.2 (s, 1 H)

EXAMPLE 54

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**2-Chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

             Obtained as a solid (16%) from the title compound of Preparation 39 and the corresponding bromide following the procedure of Example 7.

25             $\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.0$  Hz, 3 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 6.3 (s, 1 H) 7.4 (m, 3 H) 7.5 (m, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

EXAMPLE 55

30            **2-Chlorobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

             Obtained as a solid (22%) from the title compound of Preparation 39 and the corresponding bromide following the procedure of Example 1.

35             $\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.3$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.1$  Hz, 2 H) 5.3 (s, 2 H) 6.3 (s, 1 H) 7.4 (m, 3 H) 7.5 (m, 2 H) 8.4 (m, 2 H) 8.9 (s, 1 H)

EXAMPLE 56**3-Methylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (37%) from the title compound of Preparation 40 and the corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 2.3 (s, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.1 (s, 2 H) 6.3 (s, 1 H) 7.1 (m, 3 H) 7.2 (t,  $J=7.6$  Hz, 1 H) 7.8 (m, 3 H) 8.2 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (d,  $J=6.3$  Hz, 2 H)

EXAMPLE 57**3-Trifluoromethylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (21%) from the title compound of Preparation 41 and the corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 6.2 (s, 1 H) 7.6 (d,  $J=7.0$  Hz, 2 H) 7.7 (m, 5 H) 8.2 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

EXAMPLE 58**3-Trifluoromethylbenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (25%) from the title compound of Preparation 41 and the corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 2.2 (m, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.4 (s, 2 H) 6.3 (s, 1 H) 7.4 (d,  $J=5.1$  Hz, 1 H) 7.6 (t,  $J=7.6$  Hz, 1 H) 7.7 (m, 2 H) 7.8 (s, 1 H) 8.4 (m, 2 H) 8.9 (s, 1 H)

EXAMPLE 59**3-Trifluoromethylbenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (25%) from the title compound of Preparation 41 and the corresponding bromide following the procedure of Example 2.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 4.2 (q,  $J=7.3$  Hz, 2 H) 5.4 (s, 2 H) 7.1 (s, 1 H) 7.4 (dd,  $J=8.2, 4.7$  Hz, 1 H) 7.6 (t,  $J=7.6$  Hz, 1 H) 7.7 (t,  $J=7.8$  Hz, 2 H) 7.8 (d,  $J=9.8$  Hz, 2 H) 8.3 (dd,  $J=4.7, 1.6$  Hz, 1 H) 8.6 (d,  $J=2.7$  Hz, 1 H) 9.2 (s, 1 H)

#### EXAMPLE 60

##### 10 **2-(Benzylmethylamino)-ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

The title compound of Preparation 37 (100 mg, 0.32 mmol), benzyl-(2-chloroethyl)-methylamine (212 mg, 0.97 mmol) and potassium carbonate (178 mg, 1.29 mmol) are suspended in dimethylformamide (5 ml) and heated overnight at 50°C. The solvent is evaporated under reduced pressure and the residue is passed through a silica-gel column, eluting first with hexane/ethyl acetate 1:1 to 1:2 and finally with ethyl acetate, to yield 38 mg of the desired final product. Yield= 26%.

LRMS:  $m/z$  458 ( $M+1$ )<sup>+</sup>

#### EXAMPLE 61

20

##### **4-Methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (33%) from the title compound of Preparation 43 and the corresponding bromide following the procedure of Example 7.

25  $\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 3.7 (t, 3 H) 4.2 (q,  $J=7.2$  Hz, 2 H) 5.1 (s, 2 H) 6.3 (s, 1 H) 6.9 (d,  $J=8.7$  Hz, 2 H) 7.2 (d,  $J=8.7$  Hz, 2 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (d,  $J=10.4$  Hz, 2 H)

#### EXAMPLE 62

##### 30 **3-Cyanobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (23%) from the title compound of Preparation 42 and the corresponding bromide following the procedure of Example 1.

$\delta$  (DMSO- $d_6$ ): 1.3 (t,  $J=7.0$  Hz, 3 H) 2.2 (s, 3 H) 4.2 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 6.3 (s, 1 H) 7.4 (d,  $J=5.0$  Hz, 1 H) 7.6 (t,  $J=7.9$  Hz, 1 H) 7.7 (d,  $J=8.3$  Hz, 1 H) 7.8 (m, 2 H) 8.4 (m, 2 H) 8.9 (s, 1 H)

5

EXAMPLE 63**3-Cyanobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (25%) from the title compound of Preparation 42 and the corresponding bromide following the procedure of Example 7.

$\delta$  (DMSO- $d_6$ ): 1.4 (t,  $J=7.3$  Hz, 3 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 5.3 (s, 2 H) 6.3 (s, 1 H) 7.6 (t,  $J=7.9$  Hz, 1 H) 7.6 (m, 1 H) 7.8 (m, 5 H) 8.2 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

EXAMPLE 64

15

**Cyclohexyloxycarbonyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (61%) from the title compound of Preparation 37 and chloromethyl cyclohexyl carbonate following the procedure of Example 60.

$\delta$  (DMSO- $d_6$ ): 1.3 (m, 9 H) 1.6 (dd,  $J=9.3, 2.7$  Hz, 2 H) 1.8 (dd,  $J=11.0, 4.4$  Hz, 2 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 4.5 (m, 1 H) 5.8 (s, 2 H) 6.2 (s, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.9$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

EXAMPLE 65

25

**1-Cyclohexyloxycarbonyloxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (90%) from the title compound of Preparation 37 and 1-chloroethyl cyclohexyl carbonate following the procedure of Example 60.

$\delta$  (DMSO- $d_6$ ): 1.3 (m, 6 H) 1.4 (d,  $J=5.5$  Hz, 3 H) 1.6 (d,  $J=5.9$  Hz, 4 H) 1.7 (m, 4 H) 4.3 (m, 2 H) 4.5 (m, 1 H) 6.2 (s, 1 H) 6.7 (q,  $J=5.3$  Hz, 1 H) 7.8 (m, 2 H) 8.3 (d,  $J=7.8$  Hz, 1 H) 8.5 (m, 1 H) 9.3 (m, 2 H)

EXAMPLE 66

35

**2,2-Dimethylbutyryloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (89%) from the title compound of Preparation 37 and chloromethyl 2,2-dimethylbutyrate following the procedure of Example 60.

- 5  $\delta$  (DMSO- $d_6$ ): 0.6 (t,  $J=7.4$  Hz, 3 H) 1.0 (m, 6 H) 1.4 (m, 5 H) 4.3 (q,  $J=7.3$  Hz, 2 H) 5.8 (s, 2 H) 6.2 (s, 1 H) 7.8 (m, 3 H) 8.3 (d,  $J=7.8$  Hz, 1 H) 8.5 (s, 1 H) 9.3 (m, 2 H)

**EXAMPLE 67**

10 **(S)-2-Amino-4-methylpentanoyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

The title compound of Preparation 44 (0.2 g, 0.36 mmol) is dissolved in dioxane saturated with chlorhydric acid (5 ml) and stirred at room temperature for 90 min. The solvent is evaporated under reduced pressure. Ethyl ether is added and evaporated under  
15 reduced pressure, repeating this operation three more times. The residue is suspended again in ethyl ether and left at room temperature overnight. The precipitated solid is filtered and washed twice with ethyl acetate. Once dried, 170 mg of the desired final product as a dichlorhydrate are obtained. Yield= 89%.

- 20  $\delta$  (DMSO- $d_6$ ): 0.8 (d,  $J=6.7$  Hz, 6 H) 1.4 (t,  $J=7.0$  Hz, 3 H) 1.6 (t,  $J=7.0$  Hz, 2 H) 1.7 (dd,  $J=13.3, 6.7$  Hz, 1 H) 4.0 (d,  $J=5.1$  Hz, 2 H) 4.3 (q,  $J=7.0$  Hz, 2 H) 5.9 (m, 2 H) 6.4 (s, 1 H) 7.9 (m, 1 H) 8.0 (d,  $J=3.9$  Hz, 2 H) 8.4 (d,  $J=8.2$  Hz, 1 H) 8.5 (s, 1 H) 8.6 (s, 1 H) 9.5 (m, 2 H)

**EXAMPLE 68**

25 **1,3,3-Trimethylbutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (23%) from the title compound of Preparation 48 and the corresponding boronic acid following the procedure of Example 21.

LRMS:  $m/z$  451 ( $M+1$ )<sup>+</sup>.

- 30  $\delta$  (DMSO- $d_6$ ): 0.9 (m, 9 H) 1.16 (m, 3 H) 1.34 (m, 3 H) 1.4 (m, 1 H) 1.6 (s, 3 H) 1.62 (m, 1 H) 4.2 (q, 2 H) 5.0 (m, 1 H) 7.7 (m, 1 H) 7.8 (m, 1 H) 7.9 (d, 1 H) 8.1 (d, 1 H) 8.3 (s, 1 H) 9.2 (d, 2 H).

**EXAMPLE 69**

**3-Chlorobenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (27%) from the title compound of Preparation 46 and the corresponding boronic acid following the procedure of Example 21.

5 LRMS: m/Z 477 (M+1)<sup>+</sup>.

δ (DMSO-d<sub>6</sub>): 1.3 (t, 3 H) 1.5 (s, 3 H) 4.1 (q, 2 H) 5.2 (s, 2 H) 7.3 (m, 1 H) 7.4 (m, 2 H) 7.5 (s, 1 H) 7.7-7.8 (m, 2 H) 7.9 (d, 1 H) 8.2 (d, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

EXAMPLE 70

10

**3-Methoxybenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate.**

Obtained as a solid (30%) from the title compound of Preparation 47 and the corresponding boronic acid following the procedure of Example 21.

15 LRMS: m/Z 473 (M+1)<sup>+</sup>.

δ (DMSO-d<sub>6</sub>): 1.3 (t, 3 H) 1.5 (s, 3 H) 4.2 (q, 2 H) 5.2 (s, 2 H) 6.9 (m, 3 H) 7.3 (m, 1 H) 7.7-7.8 (m, 2 H) 7.9 (d, 1 H) 8.2 (d, 1 H) 8.3 (s, 1 H) 9.2 (m, 2 H).

EXAMPLE 71

20

**Octyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (12.5 %) from the title compound of Preparation 48 and the corresponding boronic acid following the procedure of Example 21.

25 LRMS: m/Z 465 (M+1)<sup>+</sup>.

δ (DMSO-d<sub>6</sub>): 0.8 (t, J=6.6 Hz, 3 H) 1.2 (m, 10 H) 1.4 (t, J=7.3 Hz, 3 H) 1.6 (m, 5 H) 4.1 (t, J=6.6 Hz, 2 H) 4.2 (q, J=7.3 Hz, 2 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, 1 H) 8.2 (d, J=8.3 Hz, 1 H) 8.3 (s, 1 H) 9.2 (s, 2 H)

30

EXAMPLE 72

**(4E)-1,5-Dimethylhept-4-en-1-yl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (1.6 %) from the title compound of Preparation 49 and the corresponding bromide following the procedure of Example 7.

35

LRMS: m/Z 463 (M+1)<sup>+</sup>.

Retention Time: 18 min.

### EXAMPLE 73

5

**Allyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate**

Obtained as a solid (7.2 %) from the title compound of Preparation 50 and the corresponding boronic acid following the procedure of Example 21.

10 LRMS: m/Z 393 (M+1)<sup>+</sup>.

$\delta$  (DMSO- $d_6$ ): 1.4 (t, J=7.0 Hz, 3 H) 1.6 (s, 3 H) 4.2 (q, J=7.0 Hz, 2 H) 4.7 (m, 2 H) 5.2 (d, J=10.4 Hz, 1 H) 5.3 (d, J=17.4 Hz, 1 H) 5.9 (m, 1 H) 7.7 (dd, 1 H) 7.8 (dd, 1 H) 8.0 (d, J=8.3 Hz, 1 H) 8.2 (d, J=8.3 Hz, 1 H) 8.3 (s, 1 H) 9.2 (d, J=3.7 Hz, 2 H)

15 The following examples illustrate pharmaceutical compositions according to the present invention.

### COMPOSITION EXAMPLES:

#### 20 COMPOSITION EXAMPLE 1

##### **Preparation of tablets**

Formulation:

Compound of the present invention	5.0 mg
Lactose	113.6 mg
25 Microcrystalline cellulose	28.4 mg
Light silicic anhydride	1.5 mg
Magnesium stearate	1.5 mg

30 Using a mixer machine, 15 g of the compound of the present invention are mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture is subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material is pulverised using a hammer mill, and the pulverised material is screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate are added to the screened material and mixed. The

mixed product is subjected to a tablet making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

## COMPOSITION EXAMPLE 2

### 5 Preparation of coated tablets

Formulation:

	Compound of the present invention	5.0 mg
	Lactose	95.2 mg
10	Corn starch	40.8 mg
	Polyvinylpyrrolidone K25	7.5 mg
	Magnesium stearate	1.5 mg
	Hydroxypropylcellulose	2.3 mg
	Polyethylene glycol 6000	0.4 mg
15	Titanium dioxide	1.1 mg
	Purified talc	0.7 mg

Using a fluidised bed granulating machine, 15 g of the compound of the present invention are mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyvinylpyrrolidone is dissolved in 127.5 g of water to prepare a binding solution. Using a fluidised bed granulating machine, the binding solution is sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate is added to the obtained granulates and mixed. The obtained mixture is subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution is prepared by suspending 6.9 g of hydroxypropylmethyl-cellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above are coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

## COMPOSITION EXAMPLE 3

### Preparation of capsules

35 Formulation:

	Compound of the present invention	5.0 mg
	Lactose monohydrate	200 mg
	Colloidal silicon dioxide	2 mg
	Corn starch	20 mg
5	Magnesium stearate	4 mg

25 g of active compound, 1 Kg of lactose monohydrate, 10 g of colloidal silicon dioxide, 100 g of corn starch and 20 g of magnesium stearate are mixed. The mixture is sieved through a 60 mesh sieve, and then filled into 5,000 gelatine capsules.

10

#### COMPOSITION EXAMPLE 4

##### Preparation of a cream

Formulation:

	Compound of the present invention	1 %
15	Cetyl alcohol	3 %
	Stearyl alcohol	4 %
	Gliceryl monostearate	4 %
	Sorbitan monostearate	0.8 %
	Sorbitan monostearate POE	0.8 %
20	Liquid vaseline	5 %
	Methylparaben	0.18 %
	Propylparaben	0.02 %
	Glycerine	15 %
	Purified water csp.	100 %

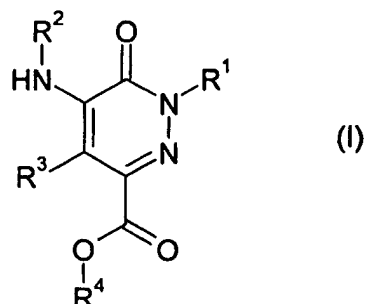
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An oil-in-water emulsion cream is prepared with the ingredients listed above, using conventional methods.

CLAIMS:

1. A compound of formula (I)

5



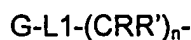
wherein

R¹ represents:

- a hydrogen atom;
- 10 • an alkyl, alkenyl or alkynyl group, which is optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups;
- 15 R² represents a monocyclic or polycyclic heteroaryl group, which is optionally substituted by one or more substituents selected from:
  - halogen atoms;
  - alkyl and alkylene groups, which are optionally substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl or mono- or di-alkylcarbamoyl groups
  - 20 • phenyl, hydroxy, hydroxycarbonyl, hydroxyalkyl, alkoxycarbonyl, alkoxy, cycloalkoxy, nitro, cyano, aryloxy, alkylthio, arylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, acyl, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulfamido, aminosulfonyl, mono- or di-alkylaminosulfonyl, cyano, difluoromethoxy or trifluoromethoxy groups;
  - 25

R<sup>3</sup> represents a hydrogen atom or an alkylcarbonyl group wherein the alkyl group may be substituted by one or more substituents selected from halogen atoms and phenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, alkylthio, arylthio, oxo, amino, mono- or di-alkylamino, acylamino, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl groups

R<sup>4</sup> represents a group of formula:



wherein

n is an integer from 0 to 3

R and R' are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

L1 is a linker selected from the group consisting of a direct bond, a -O-, -CO-, -NR"-, -

O(CO)NR"-, -O(CO)O-, -O-(CO)-, -(CO)O-, -NR"-(CO)- and -O(R"O)(PO)O- groups wherein R" is selected from the group consisting of hydrogen atoms and lower alkyl groups

G is selected from hydrogen atoms and alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, arylalkyl and heteroaryl groups said groups being optionally substituted

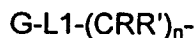
with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more substituents selected from halogen atoms; and
- hydroxy, alkoxy, cycloalkyloxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfamoyl, amino, mono- or di-alkylamino, acylamino, nitro, acyl, hydroxycarbonyl, alkoxycarbonyl, carbamoyl, mono- or di-alkylcarbamoyl, ureido, N'-alkylureido, N',N'-dialkylureido, alkylsulfamido, aminosulphonyl, mono- or di-alkylaminosulfonyl, cyano, difluoromethoxy or trifluoromethoxy groups;

and the pharmaceutically acceptable salts or N-oxides thereof

2. A compound according to claim 1 wherein R<sup>1</sup> is selected from the group consisting of hydrogen atoms and lower alkyl groups, which are optionally substituted by one or more substituents selected from halogen atoms and hydroxy, alkoxy, alkylthio, hydroxycarbonyl and alkoxycarbonyl groups.

3. A compound according to any preceding claim wherein  $R^2$  is an heteroaryl group which is optionally substituted by one or more substituents selected from halogen atoms and alkyl, hydroxy, hydroxyalkyl, hydroxycarbonyl, alkoxy, alkylendioxy, alkoxy carbonyl, aryloxy, acyl, acyloxy, alkylthio, arylthio, amino, nitro, cyano, mono- or di-alkylamino, acylamino, carbamoyl or mono- or di-alkylcarbamoyl, difluoromethyl, trifluoromethyl, difluoromethoxy or trifluoromethoxy groups;
4. A compound according to any preceding claim wherein  $R^2$  is a N-containing heteroaryl group.
5. A compound according to any preceding claim wherein  $R^2$  is optionally substituted by one or more substituents selected from halogen atoms and lower alkyl groups.
6. A compound according to any preceding claim wherein  $R^4$  represents:



wherein

n is an integer from 1 to 3

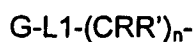
- R and R' are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

L1 is a linker selected from the group consisting of a direct bond, -O-, -O(CO)-, -(CO)O- and -O(CO)O- groups

- G is selected from alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups said groups being optionally substituted with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more substituents selected from halogen atoms; and
- hydroxy, alkoxy, cyano and cycloalkyloxy groups,

7. A compound according to claim 6 wherein  $R^4$  represents:



wherein

- n is an integer from 1 to 3

R and R' are independently selected from the group consisting of hydrogen atoms and lower alkyl groups

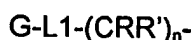
L1 is a linker selected from the group consisting of a direct bond, -O-, -O(CO)- and -O(CO)O- groups

5 G is selected from alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl groups said groups being optionally substituted with one or more substituents selected from:

- halogen atoms;
- alkyl and alkenyl groups, which are optionally substituted by one or more substituents selected from halogen atoms; and

10 • hydroxy, alkoxy and cycloalkyloxy groups,

8. A compound according to claim 7 wherein R<sup>4</sup> represents:



15

wherein

n is an integer from 1 to 2

R and R' are independently selected from the group consisting of hydrogen atoms and methyl groups

20

L1 is selected from direct bond and groups -O-, -(CO)O- and -O(CO)O-; and

G is selected from alkyl, cycloalkyl, aryl and heteroaryl groups said groups being optionally substituted with one or more halogen atoms or groups alkoxy, cyano, alkyl or -CF<sub>3</sub>;

25 9. A compound according to any preceding claim wherein R<sup>3</sup> represents a hydrogen atom or an acyl group

10. A compound according to claim 1 which is one of:

30

ethyl 4-acetyl-1-ethyl-6-oxo-5-(quinolin-5-ylamino)-1,6-dihydropyridazine-3-carboxylate

ethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate

ethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-

35

carboxylate

- ethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- isopropyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 5 benzyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- isopropyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-methylbutyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 10 2-methoxyethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- cyclopropylmethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 15 methyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 2-phenylethyl 4-acetyl-1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- benzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 20 cyclohexyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- tert-butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 cyclobutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- cyclohexyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-methyl-2-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 1-phenylethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- tert-butyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

1-phenylethyl 4-acetyl-1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

sec-butyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

5 2-(dimethylamino)-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

2-methoxy-1-methyl-2-oxoethyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

10 benzyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

ethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate

ethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

15 isopropyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate

pyridin-2-ylmethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate

isopropyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

20 ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

isopropyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

3-thienylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

25 3-thienylmethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

3-methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

30 3-methoxybenzyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate

3-chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

1-phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- 1-phenylethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-pyridin-4-ylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 1-pyridin-4-ylethyl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1-pyridin-4-ylethyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 2,3-dihydro-1H-inden-1-yl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 10 2,3-dihydro-1H-inden-1-yl 1-ethyl-5-[(4-methylpyridin-3-yl)amino]-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1,3,3-Trimethylbutyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 3-Chlorobenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Methoxybenzyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 20 Benzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- Octyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 1,5-Dimethylhex-4-en-1-yl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 Allyl 4-acetyl-1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- Benzoyloxycarbonylmethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2-Oxo-2-phenylethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 Dimethylcarbamoymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2-Phenoxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

- 2-Dimethylaminoethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Bromobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 5 4-Bromobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Bromobenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 10 2-Chlorobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2-Chlorobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Methylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 15 3-Trifluoromethylbenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Trifluoromethylbenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Trifluoromethylbenzyl 1-ethyl-6-oxo-5-(pyridin-3-ylamino)-1,6-dihydropyridazine-3-carboxylate
- 20 2-(Benzylmethylamino)-ethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 4-Methoxybenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 25 3-Cyanobenzyl 1-ethyl-5-(4-methyl-pyridin-3-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 3-Cyanobenzyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- Cyclohexyloxycarbonyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 30 1-Cyclohexyloxycarbonyloxyethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate
- 2,2-Dimethylbutyryloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

(S)-2-Amino-4-methylpentanoyloxymethyl 1-ethyl-5-(isoquinolin-4-ylamino)-6-oxo-1,6-dihydropyridazine-3-carboxylate

and pharmaceutically acceptable salts thereof.

5

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10 in admixture with a pharmaceutically acceptable diluent or carrier.

10 12. Use of a compound according to any one of claims 1 to 10, in the manufacture of a medicament for the treatment or prevention of a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4.

15 13. Use according to claim 12, wherein the medicament is for use in the treatment or prevention of a disorder which is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

20 14. A method for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by inhibition of phosphodiesterase 4, which method comprises administering to the said subject an effective amount of a compound according to any of claims 1 to 10.

25 15. A method according to claim 14, wherein the pathological condition or disease is asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis or irritable bowel disease.

16. A combination product comprising:

- 30 (i) a compound according to any one of claims 1 to 10; and  
(ii) another compound selected from (a) steroids, (b) immunosuppressive agents, (c) T-cell receptor blockers, (d) antiinflammatory drugs, (e)  $\beta$ 2-adrenergic agonists and (f) antagonists of M3 muscarinic receptors  
for simultaneous, separate or sequential use in the treatment of the human or animal body.

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 7 C07D237/24 C07D401/12 C07D401/14 C07D409/14 A61K31/50  
A61K31/501 A61P11/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/097613 A (ALMIRALL PRODESFARMA SA) 27 November 2003 (2003-11-27) cited in the application the whole document -----	1, 12



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

4 October 2005

Date of mailing of the international search report

07/11/2005

Name and mailing address of the ISA

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Authorized officer

Allard, M

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2005/006304

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03097613	A	27-11-2003	AU 2003236648 A1	02-12-2003
			BR 0310106 A	22-02-2005
			CA 2485896 A1	27-11-2003
			EP 1503992 A1	09-02-2005
			ES 2195785 A1	01-12-2003

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